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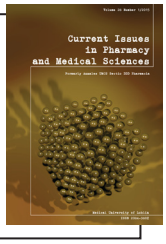

Effect of compression pressure on mechanical and release properties of tramadol matrix tablets

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ABSTRACT

Drug delivery to the proper site of action in the body is greatly influenced by the excipients used and some processing variables such as changes in compression force.

The aim of this investigation was to study the influence of changes in compression forces during tablet manufacturing on the mechanical and release properties of Tramadol matrix tablet. Hardness and friability were used as assessment parameters for mechanical properties while release properties were analysed using dissolution test. Data were analysed using One-way ANOVA at $p < 0.05$.

Tablet hardness and friability were typically compression pressure-dependent with a significant difference in tablet hardness and friability with increase in compression pressure ($p < 0.001$).

Drug release was best expressed by Korsmeyer-Peppas equation as the plots showed high linearity (r^2) of 0.998 and 0.988 for formulations containing Xanthan gum and Sodium carboxymethylcellulose, respectively. Drug release from formulations containing Xanthan gum was mainly by diffusion while a combination of diffusion and chain relaxation was the mechanism of drug release from formulation containing Sodium Carboxymethylcellulose.

The release properties of tramadol matrix tablet were not significantly influenced by compression pressure but rather by the polymer and the material properties of the drug.

INTRODUCTION

Pharmaceutical tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform quantities of particles.

Compressed tablet was invented by Thomas Brockedon over 170 years ago [23]. Since then, it has been the most popular oral dosage form [24]. The popularity of this dosage form over other forms stems from its advantages which include; accurate dosage, ease of handling and administration, good stability, cost effectiveness, easy to manufacture in large scale, good patients acceptance.

The objective of the design and manufacture of compressed tablets is to release and deliver orally the correct amount of drug in the right form, at or over the accurate time period and in the desired physiological location; and to have its chemical integrity protected to that point. Apart from the physical and chemical properties of the drug to be formulated into a tablet, the actual physical properties, manufacturing process, and complete chemical make-up of the tablet can have a profound effect on the efficacy of the drug being administered. Some of the manufacturing processes that can affect tablet quality are tabletting machine compression force and speed [16,20,25,26]. Thus, evaluation of tablet properties is an important aspect of quality control ensuring production of tablets with prompt bioavailability.

During tablet manufacturing, pharmaceutical powders are subjected to compressional forces to make a solid stable compact called tablet. These powders vary in their mechanical behaviour during compression, some deform elastically, plastically or they fragments. Elastic deformation is reversible, plastic deformation is irreversible [16] while in fragmentation, particles break-up into a number of smaller, discrete parts [9]. Deformation mechanism of materials is affected by properties of that material [26] and compression force and speed [19].

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Tablet production is a mechanical stress process involving some numbers of steps [26]. The first step is the filling of the die where rearrangement takes place. As the compression force increases, the powder becomes densely packed with no inter-particulate void spaces for any relative particle movement. At this stage, stress starts to build-up at the particle contact point in the die and the material begins to deform. Once the particles have deformed above the elastic limit of the material, even after the removal of the compression force, it becomes irreversible. But if the force is not strong enough for it to exceed the elastic limit of the particle, an unstable tablet that crumbles is formed. In tablet compression, materials have a dependant compression force limit, compression below this limit, materials will not form a coherent compact while compression above this limit, materials form a coherent tablet with increasing strength as the compression force increases. When the critical compression force limit is exceeded, tablet strength reduces and lamination and capping may develop [26].

The impacts of manufacturing conditions on tablet properties are enormous and these have to be taken into consideration to produce tablets of optimum properties. Variations in the manufacturing process could have profound effects on final tablet quality [1]. Tablet hardness, friability and dissolution are important and widely used parameters to control the tablet manufacturing process. Tablet hardness is used as a surrogate measure for compression force during manufacture – often because the tablet machine is unable to measure compression force. This is a very important control parameter because compression pressure affects tablet properties including mechanical and release properties. Tablet stability is affected in some cases.

The force used in the compression of tablets will affect the final tablet properties. Same compression force will ensure that tablets are compressed to an equal thickness [13]. Factor such as granule size, size distribution and variation in punch length will affect the precise amount of powder captured within the die. Also, an excessively high rotational machine speed will not allow the powder sufficient time to fall into the die. The variations in the amount of powder in each die result in tablets of different weights and densities, and consequently different forces will be required for compression to obtain equal thickness. Further, non-uniform compression forces can result in inconsistent tablet properties and thus affect the efficacy of the dosage form [17].

Marais *et al*. [18] showed that the magnitude of the compression force affects tablet hardness and disintegration time. An increase in compression force produces an increase or decrease in disintegration time, depending on the formulation and also increases tablet hardness.

Hence, the aim of this investigation was to evaluate the effect of changes in compression forces during tablet manufacturing on the mechanical and release properties of tramadol matrix tablet.

MATERIALS

The materials used in the investigation were Tramadol hydrochloride, a gift from Uripharm Specialties Ltd, Lagos, Lactose (DMV Veghel, Netherlands), Xanthan gum (Jungbenzlauer Ges.M.B.H. Handelsgericht Wien, Germany), Sodium carboxlmethylcellulose, a gift from Exus Pharmaceutical Ltd, Ketu-Ejinrin, Lagos. All other solvents and chemicals were of analytical grade.

METHODS

Calibration curve

Appropriate dilution of standard solution of Tramadol hydrochloride (1000 µg/ml) was prepared with distilled water to obtain dilutions of 50, 100, 150, 200 and 250 µg/ml. The absorbance of each dilution was analysed spectrophotometrically at 271 nm using Jenway UV-780 print UV-Spec. A linear equation for the dilutions and absorbance values were fitted as shown in Figure 1.

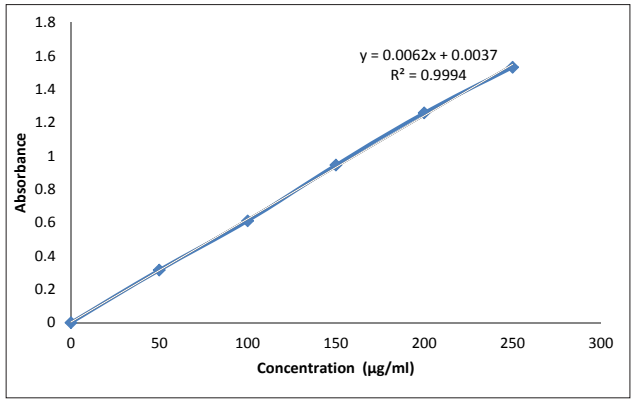

Figure 1. Calibration plot for Tramadol hydrochloride at 271 nm

Tablet formulation

Batches (400 mg) of Tramadol hydrochloride were prepared by direct compression method. All the ingredients on Table 1 were blended to form a uniform powder mix and compressed at pressures between 28.31 and 198.15 MNm^{-2} with a 10 mm punch using a hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, USA) fitted with a pressure gauge reading up to 2.5 metric tons.

Table 1. Tablet formulations

Ingredients (mg/tab)	F1	F2	F3
Tramadol hydrochloride	100	100	100
Xanthan gum	-	100	-
Sodium carboxymethylcellulose	-	-	100
Lactose	300	200	200
Total weight	400	400	400

Uniformity of weight

Twenty tablets from each batch were weighed individually and the average weight and standard deviation was calculated.

Dimensions

The thickness and diameter of twenty tablets from each batch were measured using a micrometer screw gauge and the average thickness and diameter with their standard deviation were calculated

Drug content

Drug content was determined by weighing and crushing of 10 tablets from each formulation in a glass mortar with

a pestle. Powdered tablet equivalent to 100 mg of tramadol was weighed and dissolved in 100 ml of 0.1 N hydrochloric acid for 60 min. The mixture was filtered and 1 ml of the filtrate was diluted to 100 ml using 0.1 N hydrochloric acid. The absorbance of the solution was measured at 271 nm. The drug content was determined from the calibration curve.

Hardness

Hardness was determined by using a Tablet Hardness Tester (DKB instrument, Mumbai, Model EH 01). Mean of three determinations were taken.

Friability

Friability was calculated as the percentage lost in weight of 10 tablets placed in a Tablet Friablity Apparatus (Veego Scientific Devices, Mumbai, India) which was operated for 4 minutes at 25 revolutions per minute. Mean of three determinations were taken.

Dissolution Test

The drug release study was performed using a rotating basket USP Dissolution Apparatus operated at 50 rpm. The dissolution medium was 900 ml of 0.1 N hydrochloric acid at 37±0.5°C. Five mL samples were withdrawn at specified time intervals and immediately replaced with 5 mL of fresh dissolution medium. The withdrawn sample was analysed spectrophotometrically at 271 nm using Jenway UV-780 print UV-Spec. The percentage drug released was calculated using a regression equation obtained from the calibration curve.

Analysis of dissolution data

Mean dissolution time (MDT), t_{25}, t_{50}, and $t_{75,}$ times for 25%, 50% and 75% of drug to be released were obtained from the dissolution profile and were used to characterize the drug release rate.

Drug release kinetics

To determine the release kinetics of Tramadol matrix, the data obtained from the dissolution profiles were fitted into different kinetic equations, zero-order (cumulative amount of drug release versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of drug release versus square root of time), and Korsmeyer-Peppas (log cumulative percentage of drug release versus log time) [5,11,15]. Regression equations were obtained and the correlation coefficients (r^2), release exponential, n and kinetic constant were obtained. The model with the highest correlation coefficient (r^2) was chosen as the best fit.

STATISTICAL ANALYSIS

All the parameters were analysed using Microsoft Excel 2007 and GraphPad Prism 5 software. One-way ANOVA and t-test were used to check significant differences in mean of the parameters. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS

The effect of compression force on tablet weight, dimensions, friability and crushing strength are presented in Table 2. The crushing strength and friability profile of tramadol matrix tablet are presented in Figures 2 and 3. Dissolution profile of Tramadol formulations containing Xanthan gum and Sodium carboxymethylcellulose at different compression pressure are presented in Figures 4 and 5 respectively. Effect of compression pressure on dissolution times are presented in Tables 3 and 4 while the effect of compression pressure on release parameters of tramadol matrix tablets from different release models are presented in Tables 5 and 6.

Table 2. The physical properties of tramadol matrix tablets obtained by way of different exerted compression pressures

Sample	Applied Pressure (MNm^{-2})	Thickness (mm)	Weight uniformity (g)	Crushing Strength (N)	Friability %
F1	28.29	4.62±0.03	0.412±1.49	10.2±1.94	11.87±0.02
	56.58	4.59±0.05	0.410±1.56	14.6±1.22	9.22±0.00
	84.87	4.37±0.04	0.410±1.68	15.8±1.58	7.48±0.00
	113.16	4.34±0.04	0.412±1.47	18.2±1.89	5.40±0.01
	141.45	4.31±0.02	0.410±1.64	20.6±1.56	5.08±0.00
	169.74	4.28±0.07	0.408±1.32	23.9±1.75	4.78±0.03
F2	28.29	4.29±0.04	0.414±1.10	142.2±1.23	0.82±0.01
	56.58	4.20±0.04	0.410±1.09	153.0±1.79	0.78±0.01
	84.87	4.09±0.05	0.413±1.11	167.8±1.32	0.75±0.01
	113.16	4.06±0.04	0.414±1.49	175.7±1.55	0.70±0.01
	141.45	4.02±0.02	0.414±1.11	183.5±1.96	0.67±0.00
	169.74	4.00±0.04	0.412±1.11	190.3±1.81	0.65±0.02
F3	28.29	4.33±0.06	0.414±1.19	68.9±1.90	1.22±0.01
	56.58	4.32±0.03	0.413±1.12	71.8±1.95	1.20±0.00
	84.87	4.19±0.04	0.409±1.03	74.3±1.85	1.16±0.00
	113.16	4.12±0.04	0.420±1.18	79.3±1.38	1.15±0.01
	141.45	4.05±0.02	0.414±1.12	82.7±1.42	1.13±0.00
	169.74	4.04±0.04	0.418±1.13	89.4±2.07	1.10±0.00

Table 3. Effect of compression pressure on dissolution times for tramadol tablet formulations incorporating Xanthan gum (F2)

Compression pressure (MNm^2)	t_{25}% (h)	t_{50} %(h)	t_{75} %(h)	MDT (h)
28.29	0.762	4.109	11.015	4.672
56.58	1.049	4.768	11.561	4.948
84.87	1.073	4.958	12.138	5.070
113.16	1.346	5.282	11.755	5.219
141.45	1.366	5.716	13.204	5.360
169.74	1.816	5.924	11.834	5.567

Table 4. Effect of compression pressure on dissolution times for tramadol tablet formulations incorporating Sodium carboxymethylcellulose (F3)

Compression pressure (MNm^2)	t_{25}% (h)	t_{50} %(h)	t_{75} %(h)	MDT (h)
28.29	0.032	0.388	1.681	1.226
56.58	0.038	0.430	1.785	1.264
84.87	0.046	0.475	1.855	1.280
113.16	0.050	0.496	1.895	1.292
141.45	0.076	0.604	2.024	1.333
169.74	0.087	0.647	2.092	1.361

Table 5. Effect of compression pressure on the release parameters of tramadol matrix tablets incorporating Xanthan gum, as derived from different release models (F2)

Compression pressure MNm²)	Zero order		First Order		Higuchi		Korsemeyer-Peppas		
	r²	K	r²	k	r²	kH	r²	k	N
28.29	0.673	0.168	0.878	0.168	0.983	24.448	0.994	27.962	0.411
56.58	0.745	0.151	0.908	0.151	0.994	22.940	0.997	24.457	0.458
84.87	0.736	0.147	0.891	0.147	0.986	22.544	0.989	24.217	0.453
113.16	0.806	0.139	0.929	0.139	0.994	21.734	0.994	21.507	0.507
141.45	0.786	0.132	0.911	0.132	0.996	20.987	0.996	21.496	0.484
169.74	0.882	0.124	0.964	0.124	0.991	20.111	0.998	17.626	0.586

Table 6. Effect of compression pressure on the release parameters of tramadol matrix tablets incorporating Sodium CMC, as derived from different release models (F3)

Compression pressure MNm²)	Zero order		First Order		Higuchi		Korsemeyer-Peppas		
	r²	K	r²	k	r²	kH	r²	k	N
28.29	0.644	28.992	0.955	0.872	0.945	51.952	0.988	64.968	0.277
56.58	0.654	28.640	0.949	0.829	0.944	51.274	0.985	63.587	0.285
84.87	0.669	28.485	0.949	0.804	0.949	50.941	0.984	62.401	0.298
113.16	0.676	28.372	0.947	0.789	0.950	50.710	0.983	61.808	0.303
141.45	0.713	28.135	0.956	0.748	0.964	50.164	0.986	59.209	0.335
169.74	0.724	27.925	0.953	0.724	0.964	49.740	0.984	58.122	0.345

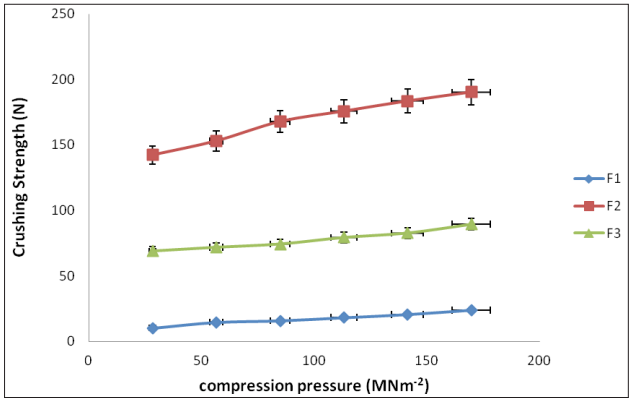

Figure 2. Effect of compression pressure on crushing strength of Tramadol matrix tablet

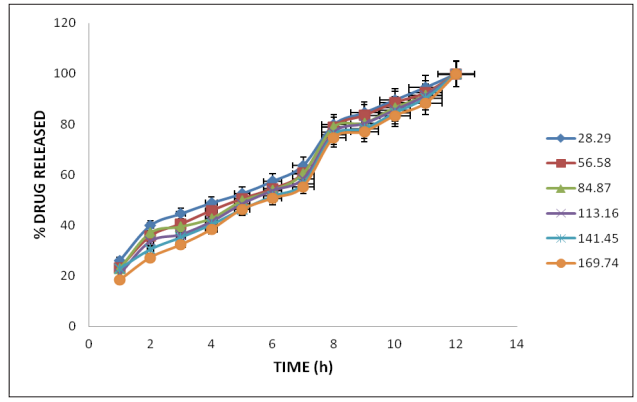

Figure 4. Dissolution profile of Tramadol formulation containing Xanthan gum at different compression pressure

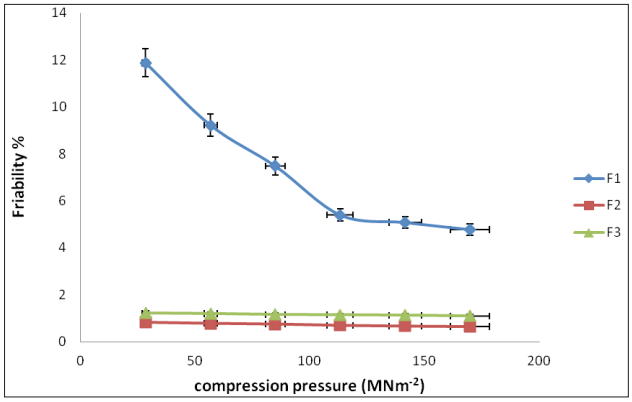

Figure 3. Effect of compression pressure on friability of Tramadol matrix tablet

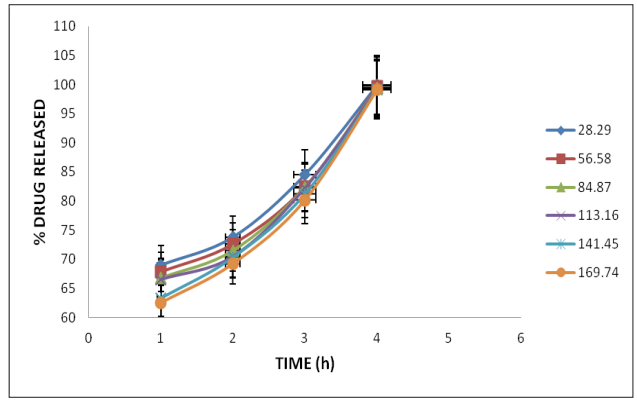

Figure 5. Dissolution profile of Tramadol formulations containing Sodium carboxymethylcellulose at different compression pressure

DISCUSSION

Effect of compression pressure on tablet dimensions

From the result on Table 2, compression pressure has no effect on the diameter of the tablet for the three formulations. This is expected only if plastic deformation has taken place as the powder bed in the die is in a confined region. The radial force is exerted on the die wall which makes the tablet to assume the diameter of the die as the axial pressure increases.

Tablet thickness reduces as compression pressure increases. This is expected as increase compression pressure tends to displace gas from a powder bed due to particle rearrangement which leads to reduction in the height of the

powder bed in the die, thereby leading to volume reduction. As pressure increases, further rearrangement is prevented, at this stage; volume reduction is accompanied by deformation [26]. However, statistically, Anova analysis shows that compression pressure had no significant effect on tablet thickness.

Effect of compression pressure on Hardness

Hardness is a measure of tablet strength. Its gives insight into the force required to break a tablet. It assesses how strong a tablet is to withstand breakage, crumbling or chipping under the conditions of storage, transportation and handling [21]. Generally, hardness is dependent on type and concentration of binder [3], tablet height to diameter ratio and compression force [10]. This study has been able to established that keeping all other manufacturing processes constant and having compression pressure as the only variable, there was a great influence on the hardness of the tablet for the three formulations. Anova analysis reveals a significant difference in tablet hardness with increase in compression pressure ($P<0.001$). This is in agreement with the study carried out by [8,10]. This could be due to gas displacement from the powder bed in the die as compression pressure increases bringing particles in close contact. This therefore causes increase in the number of particle – particle contact within the material thereby increasing particle-particle interaction leading to formation of a strong bond which increases the mechanical strength of the tablet at high compression pressure.

Friability

The friability test for tablets is used to assess the ability of the tablets to withstand shock and abrasion which will be encountered during packaging, transportation and handling [4]. The friability values were observed to decrease as pressure increases in all the formulations. This decrease could have been due to the formation of more solid bonds which led to the formation of tablets with increasing hardness and more resistance to fracture and abrasion [2, 21]. The friability values were below 1% in formulations containing Xanthan gum but above 1% in formulations containing SCMC. According to Odeku and Itiola [21], convectional tablets which loose less than 1% of their weight during the friability test are generally considered acceptable.

Effect of compression pressure on release rate

Mean dissolution time (MDT), t_{25}, t_{50}, and t_{75} were obtained from the dissolution profile in Figures 3 and 4 and were used to characterize the drug release rate. Some published articles have shown that compression does not have any effect on release properties of drugs [12,25] while some shows that it does [16,19]. In this study, it was observed that, the MDT, t_{25}, t_{50}, and t_{75} increased with increase in compression pressure for both formulations (F2 and F3). However, One way Anova statistical analysis shows that there was no significant difference in the release rate of the matrix tablets with changes in compression pressure ($p>0.05$). Drug release from matrix tablets takes place as a result of hydration when the matrix comes in contact with dissolution medium [14]. The hydrated portion leads to the formation of gel in which the drug diffuses out. The viscosity of the gel and diffusional path length of the gel layer determines the release rate rather than the compression pressure or tablet hardness [22]. It is the rate determining step in matrix tablet dissolution. While disintegration is not desirable in a matrix tablet, dissolution will occur in the system no matter how hard. The design of such delivery system is for the tablet to remain intact and gradually erodes to release its content, if that structure or design is lost, drug release is not longer controlled, and all will be release at once which can cause drug dumping. This is one of the problems of sustained release delivery. Hardness will be of importance when the tablet crumbles, from the friability, one would know that. And also since the polymers are soft, at little pressure they form solid compact because they easily undergo plastic deformation. Several authors [6,7] have stated that compression pressure is a statistically significant factor regarding tablet hardness, but its effect on drug release was found to be minimal.

Effect of compression pressure on Release kinetics

To study the effect of compression pressure on drug release, data were fitted to zero-order, first order, Higuchi and Korsmeyer-Peppas equations [5,11,15]. In this study, the drug release from the two formulations could be best expressed by Korsmeyer-Peppas equation as the plots showed high linearity (r^2) of 0.998 and 0.988 for formulation containing Xanthan gum and Sodium Carboxymethylcellulose, respectively.

The dissolution data were also fitted to Korsmeyer-Peppas equation [15] in order to describe the drug release mechanism from the matrix system. The slope n, diffusion exponential which indicates the mechanism of drug release was observed to be between 0.411 and 0.586 and 0.277 and 0.345 for formulation containing Xanthan gum and Sodium Carboxymethylcellulose respectively. For cylindrical matrix tablets, an n value ≤ 0.45 indicates a release mechanism governed by diffusion and $0.45 < n < 0.89$ indicates a release mechanism governed by combination of diffusion and macromolecular chain relaxation [14]. The n results clearly indicated that drug release is generally controlled by a combination of diffusion and chain relaxation in formulations containing Xanthan gum while in formulations containing Sodium Carboxymethylcellulose, drug release is controlled mainly by diffusion. Therefore, it can be concluded that compression pressure does not have a significant effect on release rate and mechanisms but rather polymer type. This is in accordance with previously published work by Ibrahim, and Santos [12,25]

CONCLUSIONS

There was a significant effect of compression pressure on the mechanical properties of the matrix tablets. However, the release properties of tramadol matrix tablet formulations were not significantly influenced with increase in compression pressure. It can therefore be concluded that the matrix forming polymer and the material properties of the drug had a greater influence on release properties than compression pressure.

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