

The Effect of Formulation Variables on the Release Kinetics of Paracetamol Tablet Formulations

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Abstract

The objective of this work was to study the effects of formulation variables on the release kinetics of paracetamol tablet formulation. Paracetamol tablets were formulated using wet granulation (WG) and direct compression (DC) using two predetermined pressures. Avicel, dicalcium phosphate (DCP) and pregelatinized starch (PGS) were used as directly compressible excipients for the DC method while corn starch, gelatin, and acacia were used as binders for the WG methods. Tensile strength (TS) and the dissolution times of the tablets were determined. The drug release data were fitted into different kinetic models to determine the drug release mechanism(s) for the paracetamol tablets. Noyes-Whitney plots were further used to obtain release processes for formulations having r^2 of best fit from kinetic modeling. The TS and dissolution times increased with increase in compressional pressure for all tablet formulations. The ranking of TS for tablets was starch > gelatin > acacia > avicel > DCP > PGS. Drug release kinetics indicated that the drug release was best explained by the first-order model for direct compression formulation. However, first-order and Higuchi equations gave the best fit with the highest correlation coefficient for the formulation prepared through wet granulation. Korsmeyer's plots indicated an n value ranging from 1.227 to 1.839 which indicates that the drug release mechanism from the formulations was by super case II transport. Generally, r^2 values were higher for tablets with lower compression pressures and higher for those with binders than direct compression excipients. The release kinetics of paracetamol tablets were observed to be influenced by the interplay of variables involved such as compressional pressure, formulation excipient and method. The wet granulation was also found to produce optimum release than direct compression.

Keywords: Paracetamol tablets, Release kinetics, Compression pressure, Formulation methods, Formulation excipients.

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Introduction

Drug release has been an important topic in the field of drug delivery for decades. Drug release refers to “the process in which drug solutes migrate from the initial position in the polymeric system to the polymer’s outer surface and then to the release medium” [1]. The release of drug from pharmaceutical tablets is a major determinant of its biological effect, thus evaluation of drug release kinetics is of paramount importance. Kinetic models are often used to determine release mechanisms of drugs which and are in turn used to monitor the degree of drug release. In addition, drug kinetics helps to represent release data with one or two variables [2]. Kinetic models also allow the measurement of some important physical parameters such as the drug diffusion coefficient and the determination of model fitting on experimental release data [3]. The mechanisms of drug release from tablets are dependent on many variables which include the nature of the drug, its polymorphic form, crystallinity, particle size, the rate of dissolution of soluble excipients or drug out of the tablet and the rate at which the insoluble excipients or drug in drug complex erodes [4, 5]. Several mathematical models have been published to elucidate the drug release kinetics and these include zero order, first order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas. Each model makes certain assumptions and due to these assumptions, the applicability of the respective models is restricted to certain drug–complex systems [6].

Direct compression (DC) and wet granulation (WG) represents the commonly used methods employed in the preparation of tablets. Each method has its own merits and limitations and these must be considered when a method is to be chosen for the manufacturing of pharmaceutical tablets. For instance, DC is economical compared to WG since it requires fewer unit operations while DC is more suitable for moisture and heat sensitive active pharmaceutical ingredients (APIs) since it eliminates

the wetting and drying steps associated with wet granulation thus increasing the stability of active ingredients [7]. However, DC is more prone to segregation because of the difference in density of the APIs and excipients. This may lead to problems like weight variation and poor content uniformity. Generally, only a few pharmaceutical materials can be compressed directly into tablets hence various directly compressible excipients have been manufactured to aid the formulation of tablets with satisfactory mechanical and dissolution properties [8]. Paracetamol, a potent analgesic, is a sparingly soluble drug with poor flow properties as indicated in its inability to flow through a 13 mm diameter glass funnel [9]. It, therefore, requires a binding agent among other excipients to form satisfactory tablets.

Recently, we investigated the effect of formulation methods on the mechanical and release properties of paracetamol tablets [10]. The results indicated that there was an improved balance between the mechanical and disintegration properties of paracetamol tablets produced through wet granulation than those produced through direct compression. This suggested that WG with carefully selected drug excipients may be a preferred method over direct compression in paracetamol tablet formulation. However, it is needful to examine the effect of formulation variables on the release kinetics of paracetamol tablets to further establish the results of the previous work. In this study, therefore, the effect of formulation method, compressional pressure and type of excipients on the release kinetics of paracetamol tablet was examined.

Materials and Methods

Materials

The following materials were used: Paracetamol BP (BDH Chemicals Ltd, Poole England), Avicel® PH- 102 (FPC Biopolymer, USA), Dicalcium Phosphate dihydrate (Mendell

Co Ltd, Surrey, UK), Corn Starch BP (BDH Chemicals Ltd, Poole England), Potassium Dihydrogen Phosphate (Kermel, USA), Pregelatinized Starch (BDH Chemicals Ltd, Poole England), Disodium Hydrogen Phosphate (Kermel, USA), Magnesium Stearate (Hopkin and Williams, Chadwell, Health, Essex, UK), Acetone (Hopkin and Williams, Chadwell, Health, Essex, UK), Lactose (BDH Chemicals Ltd, Poole England), Gelatin (BDH Chemicals Ltd, Poole England), Deionized water (May & Baker Nig. Plc). All other chemicals used were of analytical grade.

Preparation of granules for wet granulation method

Batches of granules with a basic formulation containing 85 %w/w paracetamol (drug), 5 %w/w lactose (filler) and 5 %w/w cornstarch (disintegrant) were prepared using wet granulation method. The materials were accurately weighed and mixed for about 5 minutes in a Kenwood planetary mixer. Thereafter, the mixture was then moistened with the appropriate amount of 4 %w/w concentration of binder solution (acacia, gelatin or cornstarch) until a coherent mass was formed. The wet masses were granulated by passing them manually through a 1,400 μm mesh size sieve and dried in a hot air oven for 18 hr at 60 °C. The dried granules were sieved and granules with particle size ranging from 500-1000 μm were collected for the preparation of the tablets.

Preparation of powder mixtures for direct compression

The required amounts of drug (paracetamol), lubricant (magnesium stearate) and the directly compressible excipients (avicel, dicalcium phosphate (DCP) or pregelatinized starch (PGS)) were thoroughly mixed and stored in an airtight container.

Preparation of tablets

The granules or powder mixtures were compressed with predetermined loads of 56.6

and 113.2 MNm⁻² for thirty seconds using a Carver Hydraulic Hand Press (Model C, Carver Inc, Menomonee Falls, WI, USA). After ejection, the tablets were stored over silica gel for 24 hours to allow hardening and elastic recovery before evaluation. Paracetamol tablet composition is shown in Table 1 and formulation code for tablets produced via wet granulation is designated A-F and G to L for directly compressed tablets.

Determination of Tensile Strength

The tensile strength (TS) of the tablets was calculated using the equation:

$$TS = 2L / \pi dh \quad (1)$$

Where L is the load needed to cause a fracture in Newton, d and h represent the tablet diameter and thickness respectively in millimeters.

Disintegration and Dissolution test

Disintegration times of tablets were determined in distilled water at 37 ± 0.5 °C using a disintegration tester (Tab-Machines, India). The dissolution of the tablets was determined at the same temperature (37 ± 0.5 °C) in 900 ml of phosphate buffer solution pH 5.8 using a Dissolution Test Apparatus (DA-6D, Veego Scientific Devices Mumbai, India), with the rotating basket positioned 25 mm above the bottom of the flask. The machine was operated at 50 rpm to ensure no clogging of the baskets by tablet fragments. Samples (5 ml) were withdrawn at different time intervals and replaced with equal amounts of fresh medium. The sample was diluted and the amount of paracetamol released was determined using a UV spectrophotometer (Cecil CE 3021, Cecil Instrument, UK) at 249 nm. All determinations were done in triplicate.

Modelling and comparison of release profiles

Release Kinetics

To analyze the kinetics and mechanism of drug release from the tablets, data obtained from the

Table 1. Composition of Paracetamol Tablet Formulations

Formulation Code	A	B	C	D	E	F	G	H	I	J	K	L
Compressional pressure (MNm-2)	56.6	113.2	56.6	113.2	56.6	113.2	56.6	113.2	56.6	113.2	56.6	113.2
Composition (% w/w)												
Paracetamol	85	85	85	85	85	85	84	84	84	84	84	84
Lactose	5	5	5	5	5	5	-	-	-	-	-	-
Gelatin	4	4	-	-	-	-	-	-	-	-	-	-
Acacia	-	-	4	4	-	-	-	-	-	-	-	-
Corn Starch	5	5	5	5	9	9	-	-	-	-	-	-
Avicel	-	-	-	-	-	-	15	15	-	-	-	-
Emcompress	-	-	-	-	-	-	-	-	15	15	-	-
Pregelatinized starch	-	-	-	-	-	-	-	-	-	-	15	15
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total (%)	100	100	100	100	100	100	100	100	100	100	100	100

release studies were fitted to various kinetic equations. The drug release data were fitted to zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models. The model of best fit was identified by comparing the values of correlation coefficients.

Zero-order model of drug release describes the systems where the rate of drug release is independent of its concentration [11] and can be represented by the equation:

$$C = C_0 + k_0t \quad (2)$$

Where C is the amount of drug released at time t, C₀ is the initial concentration of the drug, and k₀ is the zero-order dissolution constant expressed in the units of concentration per time. The first-order model of drug release describes systems in which the release rate is dependent on the concentration [12]. Equation 3 is the mathematical expression of the model.

$$\ln C = \ln C_0 + k_1t \quad (3)$$

Where C is the amount of drug released at time t, C₀ is the initial concentration of drug, and k₁ is the first order dissolution constant

Higuchi model of drug release describes the release of drugs from the insoluble matrix as a square root of time-dependent process based on Fickian diffusion [13]. The model is used to study the release of water-soluble or poorly soluble drugs incorporated in semi-solid and/or solid matrices. The model is represented by the equation:

$$C = k_H t^{1/2} \quad (4)$$

Where C is the amount of drug release at time t and k_H is the Higuchi release constant.

Hixson-Crowell model of drug release describes the release from systems where there is a change in surface area and diameter of particles or tablets [14]. Equation 5 is the mathematical expression of the model.

$$C_0^{1/3} - C_t^{1/3} = k_H C t \quad (5)$$

Where C_0 is the initial amount of drug in the pharmaceutical dosage form, C_t is the remaining amount of drug in the pharmaceutical dosage form at time t and k_{HC} is a constant incorporating the surface volume relation.

Korsmeyer – Peppas model of drug release [15] is described by the equation 6

$$C_t / C_a = kkt^n \quad (6)$$

Where C_t / C_a is the fraction of the drug released at time t , k is the rate constant and n is the release exponent or diffusional exponent which indicates the mechanism of drug release. To determine the mechanism of drug release, first 60 % drug release data were fitted in Korsmeyer-Peppas model. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $n < 0.89$ to non-Fickian (anomalous) transport, $n = 0.89$ to Case II relaxational (zero-order release) transport, and $n > 0.89$ to super case II transport.

Description of release processes from the excipients

Tablet formulations (A, C, G and I) which had highest correlation coefficients (> 0.98) were used in plotting the first order and Noyes-Whitney plots. The integrated form of the equation of Noyes and Whitney [16] is shown below:

$$\ln [C_s / (C_s - C)] = kt \quad (7)$$

Where C_s is the concentration of the solute at saturation, C is the concentration at time t and k is a dissolution rate constant. Values of $\ln [C_s / (C_s - C)]$ were plotted versus t [17]. Values of t_1 , t_2 , and k_1 , k_2 or k_3 as the case may be were obtained from the plots.

Data Analysis

Each experiment was done in triplicate and the data expressed as a mean \pm standard error of the mean. The statistical analysis was carried out using the analysis of variance (ANOVA)

on SPSS 16.0 (IBM Corporation, New York, USA) to compare the differences between formulations. The confidence interval was set at 95 % and $p \leq 0.05$ was considered significant. For kinetic modeling, regression coefficients were used to determine the model of best fit for the formulations.

Results and Discussion

Tensile strength and dissolution times

The dissolution times at a different interval of paracetamol tablets containing different excipients are also shown in Table 2. The dissolution times, t_{15} , t_{25} , t_{50} and t_{75} (time for 15, 25, 50 and 75 % drug release respectively) generally increased with increase in compressional pressure in the tablet formulations. There were no significant differences ($p > 0.05$) in the dissolution times for formulations A, C, G and I although, tablets prepared using avicel had the lowest values. Avicel is freely soluble and will dissolve in the medium easily, thereby providing a pathway for diffusion of drug leading to the faster dissolution of the drug from the tablet [18].

Kinetic Models

Kinetic study of drug release from dosage forms is useful as they influence the dosage interval, bioavailability, overall patient adherence and the occurrence of toxic and untoward effects. In addition, kinetic parameters can be used to study the influence of formulation factors on the drug release for optimization as well as control of release [19]. The criterion for selecting the most appropriate model was on the basis of goodness of best fit which was determined by the highest correlation coefficient. The kinetic parameters and correlation coefficient (r^2) derived from the equations are presented in Tables 3 and 4.

Generally, tablets prepared by WG yielded r^2

Table 2: Tensile strength and dissolution times of paracetamol tablets

Formulation code	Binder/ Excipient	Method	Tensile strength MNm ⁻²	t15 (min)	t25 (min)	t50 (min)	t75 (min)
A	Gelatin	WG	0.544	3.0	6.0	13.0	20.0
B		“	1.025	6.0	8.0	16.0	23.0
C	Acacia	“	0.660	4.0	6.0	13.0	21.0
D		“	0.943	5.0	8.0	16.0	24.0
E	Corn Starch	“	0.896	5.0	8.0	17.0	26.0
F		“	1.306	7.0	10.0	20.0	30.0
G	Avicel	DC	0.267	2.0	5.0	12.0	20.0
H		“	0.495	5.0	7.0	14.0	21.0
I	Dicalcium Phosphate	“	0.196	3.0	5.0	13.0	22.0
J		“	0.319	4.0	7.0	15.0	23.0
K	Pregelatinized Starch	“	0.137	3.0	5.0	14.0	23.0
L		“	0.231	5.0	9.0	16.0	25.0

Table 3: Drug Release Parameters Obtained by Fitting Release Data for Paracetamol Tablets Produced via Wet Granulation into the Different Release Kinetics Models

Formulation Code	Zero-order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	r2	K ₀ (min ⁻¹)	r2	K ₁ (min ⁻¹)	r2	K _H (min ^{-1/2})	r2	K _{HC} (min ^{-1/3})	r2	n value	K _K (min ⁻ⁿ)
A	0.892	4.953	0.994*	2.321	0.954	47.470	0.780	2.395	0.902	1.344	1.864
B	0.956	5.780	0.961	2.302	0.986*	51.546	0.855	2.808	0.941	1.568	2.213
C	0.903	3.753	0.994*	2.282	0.962	47.784	0.790	2.445	0.907	1.361	1.899
D	0.912	0.080	0.979*	2.127	0.964	46.660	0.808	2.686	0.920	1.464	2.102
E	0.909	2.22	0.985*	2.078	0.966	39.626	0.763	2.702	0.874	1.508	2.187
F	0.945	1.780	0.973	2.082	0.980*	40.827	0.814	2.875	0.901	1.548	2.295

*Values from 0.98 upwards.

values which were significantly higher ($p < 0.05$) than from DC. The results further showed that the first-order ($r^2 = 0.985-0.994$) and Higuchi equations ($r^2 = 0.954-0.986$) gave the best fit for the formulations made through WG while the drug release for tablets prepared by DC fitted the first order model with r^2 ranging between 0.946 - 0.989. This indicates that the release of the drug from the tablet formulations prepared

by both methods is dependent on the concentration of drug in the formulation, while the ones prepared through WG included the square root of time dependent process based on Fickian diffusion. This is consistent with previous reports on release kinetics of paracetamol formulations [9].

In addition, three formulations (A, C, and E) prepared by WG and three (G, H and I) made

Table 4: Drug Release Parameters Obtained by Fitting Release Data for Paracetamol Tablets Produced via Direct Compression into the Different Release Kinetics Models

Formulation Code	Zero-order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	r2	K ₀ (min ⁻¹)	r2	K ₁ (min ⁻¹)	r2	K _H (min ^{-1/2})	r2	K _{HC} (min ^{-1/3})	r2	n value	K _K (min ⁻ⁿ)
G	0.861	8.920	0.989*	2.318	0.927	42.389	0.786	2.186	0.920	1.158	1.610
H	0.939	0.247	0.983*	2.312	0.973	51.530	0.872	2.464	0.965	1.246	1.770
I	0.912	6.520	0.982*	2.167	0.964	40.713	0.834	2.251	0.946	1.120	1.600
J	0.911	2.753	0.967	2.129	0.960	43.536	0.838	2.446	0.948	1.227	1.772
K	0.875	6.887	0.946	2.088	0.939	38.339	0.796	2.320	0.925	1.176	1.693
L	0.903	0.520	0.957	2.106	0.948	44.153	0.841	2.582	0.949	1.281	1.876

*Values from 0.98 upwards.

by DC followed first order with r2 >0.98. Generally, formulations with lower compression pressure (56.6 MNm⁻²) yielded higher r2 values as exemplified by A, C, E, G and I which were compressed using the lower pressure.

Representative first order plots of formulations A, C, G and I was presented in Figure 1. The plots showed that drug release depends on the concentration remaining at time t.

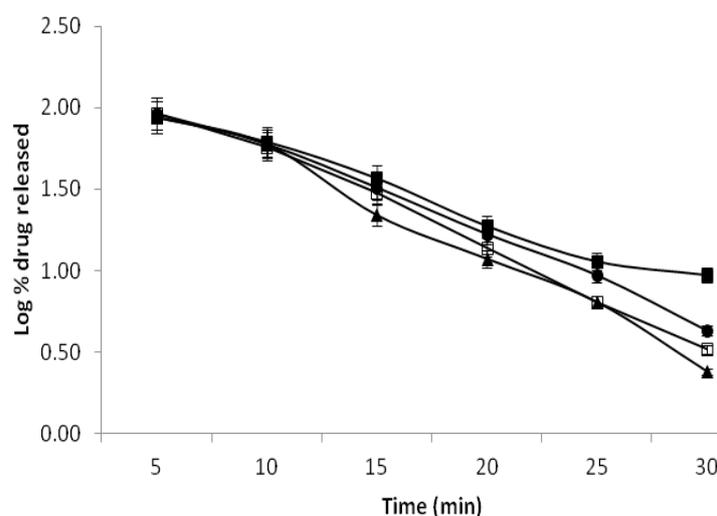


Figure 1: Representative first order kinetic model plots for paracetamol formulations compressed at 56.63 MNm⁻² ▲ avicel (r2= 0.989), □ gelatin (r2= 0.994), ● acacia (r2= 0.994), ■ DCP (r2 = 0.982).

To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas model equation which gave a release exponent (n) values ranging from 1.227 to 1.839 which indicates that the drug release mechanism from the formulations was by super case II transport,

in which a pronounced acceleration in drug release from the formulation occurred towards the latter stages of release, resulting in a more rapid relaxation-controlled transport [20]. It was also observed that the release parameters, n, increased with increase in compression pressure.

sional pressure for all the tablet formulation and the n value for tablets formulated by wet granulation were consistently higher than those produced via direct compression method. This showed that the method of tablet preparation affects release parameters and wet granulation produces tablets with improved release properties.

The release processes were further described using the Noyes-Whitney plots in Figure 2 [21, 22]. Tablets containing gelatin and acacia produced two straight regression lines with

slopes k 1 and k 2, while avicel and DCP presented three straight lines showing an additional slope of k3. The time at which the lines intersect is denoted by t 1 and t2 as the case may be. The results are presented in Table 5. The values of k1 were less than k2 denoting faster drug dissolution rate after t1. Previous reports [17, 23] have shown that the change in dissolution rate from k 1 to k2 at time t1 is owing to a change in surface area which is caused by the breaking up of tablets into fragments.

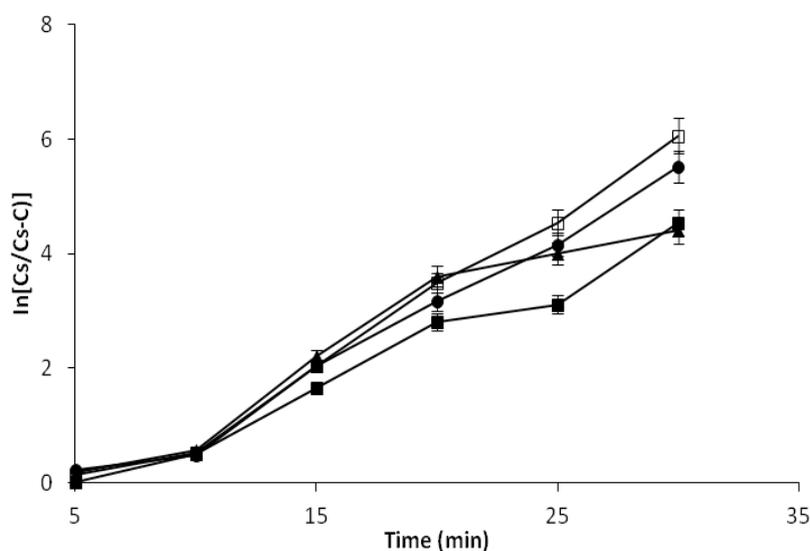


Figure 2: $\ln[C_s/(C_s-C)]$ vs time plots for paracetamol tablets compressed at 56.63 MNm⁻²
 ▲ avicel (r² = 0.979), □ gelatin (r² = 0.984), ● acacia (r² = 0.982), ■ DCP (r² = 0.985).

Table 5: Release parameters derived from Noyes-Whitney plots

Formulation code	Type of method	Binder/ Excipient	t1 (min)	t2 (min)	k1	k2	k3
A	WG	Gelatin	10	-	0.077	0.271	-
C	WG	Acacia	10	-	0.054	0.244	-
G	DC	Avicel	10	20	0.081	0.303	0.080
I	DC	DCP	10	20	0.096	0.187	0.220

Conclusion

The release kinetics of paracetamol tablets were observed to be influenced by the interplay of variables involved in compressional pressure, formulation excipient and method. The wet granulation was also found to produce optimum release than direct compression.

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