Evaluation of the mechanical and release properties of lactose and microcrystalline cellulose and their binary mixtures as directly compressible excipients in paracetamol tablets.

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ABSTRACT

Binary mixtures of microcrystalline cellulose MCC (A), and lactose (L) in ratios at 75:25, 50:50, and 25:75% respectively were prepared. The binary mixtures were subjected to microscopical analysis and density measurements. The mechanical properties of paracetamol tablets formulated with the above excipients were assessed for tensile strength, bonding capacity (using the Ryshkewitch-Duckworth relation) and friability, while drug release properties were assessed for disintegration and dissolution times. The dissolution profiles were fitted into dissolution model equations to determine release mechanism and similarity of release. Microscopic analysis showed that the lactose particles were large, crystalline, and acicular in shape whereas the MCC particles were smaller and irregularly shaped. The binary mixtures had particle shape and sizes in between the parent compounds. The particle size of A25:L75 however, was larger than that of the proprietary brand, Microcelac®. Bulk and tapped densities increased with increasing amounts of MCC in the binary mixtures while particle density had an inverse relationship. Tablets containing A75:L25 had the highest tensile strength and bonding capacity and lowest friability in comparison to other binary mixtures and Microcelac®. However, tablets containing A75:L25 did not show superiority to Microcelac® in terms of paracetamol release. Its release, however, followed the Korsmeyer-Peppas model indicating a super case II transport mechanism. Only comparisons of tablet combinations of Lactose: A25:L75 and MCC: A50:L50 had a similarity factor, f2 >50. Tablets made of A75:L25 exhibited the highest mechanical and release properties of the binary mixtures, as directly compressible excipient in comparison to the parent compounds and Microcelac®. This mixture, A75:L25 therefore, could be developed for commercial use in tablet formulations.

KEY WORDS: Lactose, microcrystalline cellulose, MCC, binary mixtures, directly compressible excipients, co-processed, Microcelac®, paracetamol

INTRODUCTION

Drug delivery systems rely entirely on the inclusion of appropriate types, grades, and concentrations of excipients in the drug manufacturing process (1). Such excipients may include pre-processed and co-processed excipients that provide added functionalities to a drug formulation, or multifunctional excipients that play multiple roles in the formulation e.g., Ludipress® that can function as a directly compressible diluent, binder, and disintegrant (2). Improving drug formulation by reducing the investment in excipients is important as pharmaceutical industries continue to need new excipients due to the increasing number of new drug moieties with varying physicochemical properties.

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Excipients with multiple functions are preferred as several processes are eliminated, thereby improving efficiency, lowering cost, and reducing production time. Additionally, multifunctional and/or highly functional excipients perform better in high-speed tableting machines and in direct compression, which has become the preferred mode of formulating tablets due to cost-effectiveness and simplicity (3).

Co-processing in the pharmaceutical industry is defined as the process of combining two or more existing excipients by an appropriate process resulting in an excipient with improved properties compared to the simple physical mixtures of the components with added value related to the ratio of its functionality or price (1). Co-processing is a relatively simple process that involves the physical mixing of two or more excipients in form of either a homogenous dispersion or solution followed by co-drying, co-precipitation, or co-crystallization, resulting in highly functional and more stable excipients (5). Co-processed excipients are altered physically without changing their chemical structures (1), making it possible for new excipients to be brought into the market without undergoing rigorous safety testing of a completely new chemical (4). The physical components of the excipients interact at sub-particulate level to provide a synergy of functionality improvements resulting in better properties than the single physical mixtures of their components. For example, Microcelac® is a proprietary brand of a co-processed excipient made up of a combination of microcrystalline cellulose and lactose at the ratio of 25:75%.

In the present study, the functionality of the combination of the physical mixtures of microcrystalline cellulose and lactose as directly compressible excipients is compared to a proprietary brand of co-processed microcrystalline cellulose and lactose, that is, Microcelac®. Tableting and drug release properties of paracetamol tablets prepared with the binary mixtures were evaluated to determine the effect of co-processing on the direct compression properties of the excipients.

MATERIALS AND METHODS

Materials

The materials used were Microcelac® 100 (Meggle Excipients and Technology, Wasserburg, Germany), microcrystalline cellulose (Avicel® PH-101, DuPont Biopolymer, Newark, DE, USA) and Paracetamol B.P. (acetaminophen, BDH Chemicals Ltd, Poole, England). All other reagents were of analytical grade.

Preparation of binary mixtures of the excipients

Batches (100 g) of microcrystalline cellulose (MCC) and lactose were mixed in proportions of 75:25, 50:50 and 25:75% in a tumble mixer (Forster Equipment Co. Ltd, Whetstone, Leicester, England) fitted with a cylindrical container with a capacity of 500 mL, and rotated at 50 RPM for 10 minutes.

Characterization of excipients

Particle size determination

The particle sizes in the excipients were determined using an optical microscopy (Olympus model 312545, Japan) for 100 particles of each excipient and the mean particle size was calculated. The photomicrographs of the excipients and their binary mixtures were taken with TSView® Software (Tucsen Imaging Technology Co., Ltd. Fujian, China) for imaging at a magnification 100x.

Density determinations

Particle densities of the excipients and binary mixtures were determined using the liquid pycnometer method using xylene, a non-solvent, as the displacement fluid (6).

The bulk densities of the excipients and their binary mixtures at zero pressure (loose density) were determined. 10 g of powder was poured at an angle of 45° through a funnel into a glass-measuring cylinder with a volume of 50 mL. The relative density (D) was obtained from the ratio of bulk density to particle density (7).

The tapped density was obtained by applying 100 taps at a standardized rate of 38 taps per minute (British Standard 1460) to 10 g of the powder sample in a graduated cylinder. All experiments were carried out in triplicate.

Properties of flow

The flowability of the excipients was assessed using the Hausner ratio (Equation 1) and Carr's index (Equation 2).

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density} \quad \text{Eq. 1}$$

$$Carr's\ index = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} x100 \quad \text{Eq. 2}$$

To determine the angle of repose of the excipients and their binary mixtures, 10 g was allowed to flow freely through a funnel under gravity; to form a conical heap. The angle of repose was calculated using Equation 3:

$$\text{Tan}\,\theta = \frac{h}{r} \quad \text{Eq. 3}$$

Where, h is the height of the powder in cm and r is the radius at the base of the cone in cm. The angle of repose was calculated from the mean of three determinations.

Preparation of tablets

Paracetamol tablets (500 mg) containing either the excipients or their binary mixtures were compressed for a minute using a Carver hydraulic press (Model C, carver Inc, Menomonee Falls, Wisconsin, U.S.A), fitted to a pressure gauge reading up to 2 tonnes. Before each compression, the punches and die were lubricated with a $2\%^{w}/_{v}$ dispersion of magnesium stearate in ethanol:ether (1:1). The tablets formed were subsequently evaluated after 24 hours.

Evaluation of the tablets

Mechanical properties

The tensile strength (T) of the tablets was determined by diametral compression using a DBK hardness tester (DBK Instruments, Mumbai, India) and calculated using Equation 4 (7):

$$\text{Tensile Strength} = \frac{2L}{\pi dt_t} \quad \text{Eq. 4}$$

where, L is the load (MN) that will cause a fracture, and d and tt are tablet diameter (m) and tablet thickness (m), respectively.

The bonding capacity, $\varkappa$, was obtained using the Ryshkewitch-Duckworth relation shown in Equation 5 (8-9):

$$\ln T = \ln T_0 - \kappa\varepsilon \quad \text{Eq. 5}$$

where, T_0 is tensile strength at zero porosity and ε is tablet porosity (1 – D), D is the relative density.

The percent friability of the tablets was determined using a friability test apparatus (DBK, Mumbai, India) at 25 RPM for 4 minutes.

Drug release profile

The disintegration time of the tablets was determined in distilled water at 37 ± 0.5°C using a disintegration tester (DBK tablet disintegration test apparatus, Mumbai, India).

The dissolution test was carried out using the USP XX III basket method rotated at 100 RPM in 900 mL of 0.1 M HCl, maintained at 37 ± 0.5°C. Samples (5 mL) were withdrawn and replaced with equal amounts of fresh medium at pre-determined time intervals. The sample was diluted and the amount of paracetamol released was determined using a UV-visible spectrophotometer (Spectrum lab 752s UV-VIS spectrophotometer, China) at a wavelength of 249 nm. Determinations were carried out in triplicate.

The drug release data were fitted into zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell,

and Hopfenberg equations to determine the kinetics and mechanism of drug release. Values of correlation coefficient were used to identify the model of best fit. The similarity factor, f_2 of the dissolution profiles of the paracetamol tablets were compared using DD Solver (Microsoft Excel add-in, Excel, 2016). Dissolution profiles with values of f_2 between 50 and 100 showed similarity to identical profiles.

RESULTS AND DISCUSSION

Particle size morphology

The mean particle sizes of the excipients and their binary mixtures are shown in Figure 1. The mean particle size for the binary mixtures increased with increasing lactose. The particle sizes of the binary mixtures fell between that of the parent compounds. However, the mean particle size of the binary mixture A25:L75 was greater than that of Microcelac®, a co-processed (spray-dryed) excipient that contained the same proportion of MCC and lactose.

The photomicrographs of the excipients and their binary mixtures are shown in Figure 2. The particles of lactose were crystalline and acicular while that of microcrystalline cellulose (MCC) was irregular. The binary mixtures exhibited both crystalline and irregularly shaped particles. As the concentration of lactose increased in the mixture, more crystalline shaped particles became evident. Particles of Microcelac® were spherical with irregular surfaces. It has been shown that irregularity of shape increases mechanical interlocking of particles which reduces the packing tendencies of the particles to a minimum such that, in some cases, the addition of more ovoid-shaped particles like starch decreases flow and enhances cohesiveness of the mixtures (10-11).

Density measurement

The particle densities of the excipients and the binary mixtures are presented in Table 1. Particle density has been shown to affect the compaction behavior of powders as dense, hard materials may require compression pressure to produce cohesive but usually less friable tablets (12). It is also one of the major contributors to the differences in packing behavior

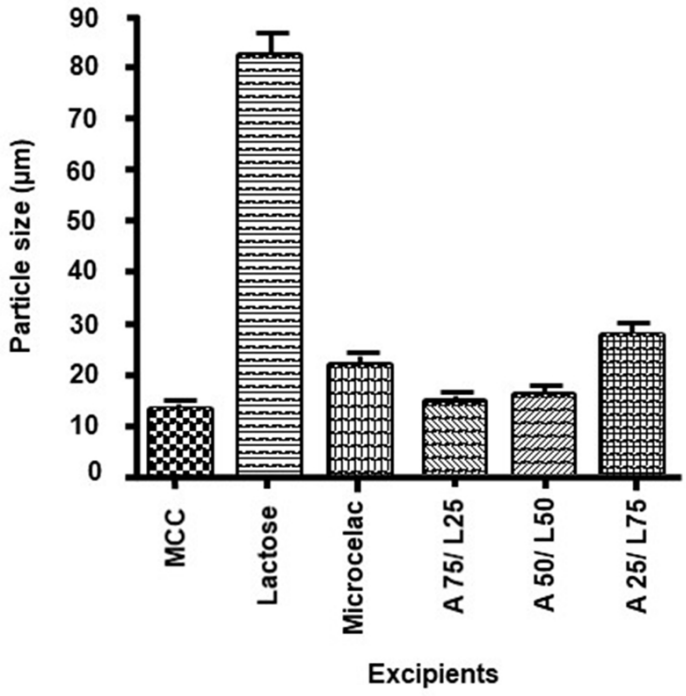

Figure 1 Mean particle size of MCC, lactose, their binary mixtures, and Microcelac®.

Table 1 Physico-chemical properties of the excipients

EXCIPIENTS	PARTICLE DENSITY (g/cm³)	BULK DENSITY (g/cm³)	TAPPED DENSITY (g/cm³)	ANGLE OF REPOSE (°)	HAUSNER RATIO	CARR'S INDEX (%)
Lactose (L)	1.222 ± 0.000	0.62 ± 0.14	0.73 ± 0.12	58.56 ± 11.13	1.17 ± 0.06	14.48 ± 6.59
A25:L75	1.134 ± 0.022	0.49 ± 0.00	0.66 ± 0.00	56.73 ± 1.20	1.36 ± 0.00	26.40 ± 0.00
A50:L50	1.229 ± 0.001	0.43 ± 0.00	0.63 ± 0.00	55.83 ± 2.84	1.45 ± 0.00	31.20 ± 0.00
A75:L25	1.359 ± 0.003	0.38 ± 0.01	0.52 ± 0.00	51.47 ± 0.00	1.30 ± 0.00	23.20 ± 0.00
MCC (A)	1.488 ± 0.006	0.30 ± 0.00	0.40 ± 0.00	56.01 ± 0.00	1.33 ± 0.00	24.90 ± 0.00
Microcelac®	1.364 ± 0.070	0.46 ± 0.00	0.58 ± 0.00	53.23 ± 0.00	1.26 ± 0.00	20.69 ± 0.00

of formulation materials during the various unit operations of tableting such as, granulation, mixing, die filling, and compressibility especially at the initial phase of compression prior to the phases of elasto-plastic flow (13). Materials with low particle density at a given pressure would yield more cohesive compacts than those with higher densities. The particle densities of the binary mixtures were lower than that of MCC. This indicated that the mixtures and lactose are more cohesive than MCC and would readily form tablets at lower compression pressures. It has also been shown that particle size affects particle density, as an increase in particle size results in decreasing particle density (14). This was observed in the results, with MCC having the lowest particle size and highest particle density while lactose with the highest particle size also had a low particle density.

The bulk density of a powder depends primarily on the particle size distribution, particle shape, and the tendency of the particles to adhere to one another (15). While tapped density indicates the rate and extent of packing that would be experienced by various unit operations of tableting (16). A high density is advantageous in tableting because of a reduction in fill volume of the die (17). Tapped density decreased with

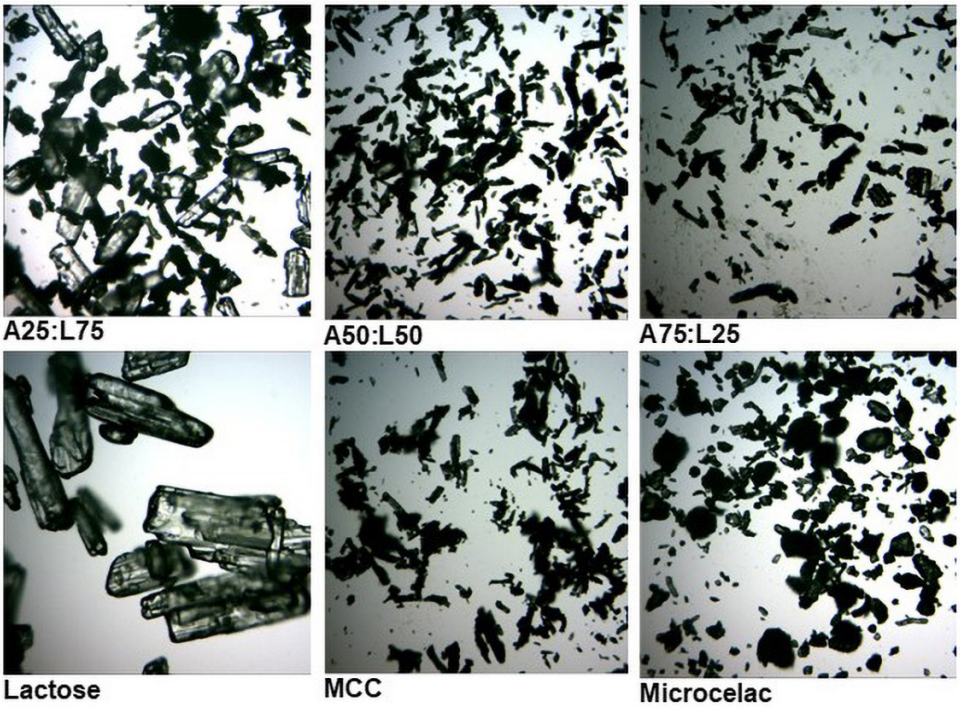

Figure 2 Photomicrographs of the excipients and their binary mixtures (magnification 100x)

Table 2 Mechanical and release properties of the paracetamol tablet formulations at relative density of 0.90/ porosity of 0.1

EXCIPIENTS	TENSILE STRENGTH (MNm^{-2})	FRIABILITY (%)	BONDING CAPACITY	DISINTEGRATION TIME (MIN)	DISSOLUTION TIME (MIN)	
					t_{50}	t_{80}
Lactose (L)	1.500	0.16	3.67	-	-	-
A25:L75	1.050	0.14	6.49	16.8	-	-
A50:L50	1.280	0.09	10.26	1.4	47.5	-
A75:L25	1.900	0.04	10.84	45.0	30.2	50.0
MCC (A)	3.370	0.01	4.76	27.0	39.0	-
Microcelac®	1.320	0.05	12.63	0.2	21.0	42.2

a decrease in the concentration of lactose in the binary mixtures. However, tapped density values were all greater than that of MCC implying a better reduction in fill volume. Tapped density of A25:L75 was also higher than that of Microcelac®. The difference in tapped densities is probably due to differences in particle size distribution and particle shape, which was spherical with irregular surfaces for Microcelac® as seen from the photomicrographs and which is known to affect the packing arrangement of particles.

Flow properties

The angle of repose, Carr's index, and Hausner ratio are also presented in Table 1. The angle of repose is a derived property and a qualitative measure of cohesiveness or the tendency of the powdered or granulated materials to flow, for example, from the hopper through to the feed frame into the tableting machine. Generally, the rougher and more irregular the surface of the particles, the higher the value of the angle of repose (11). Such uniformity of flow will minimize weight variations in the tablets produced (18). The angle of repose of 30° and below is usually an indication that the powder is free-flowing and the angle of repose greater than 40° indicates poor flow (19).

The angle of repose for the excipients ranged between 51 and 59° indicating poor flow properties. In the binary mixtures, however, the flow seemed to improve with an increase in the concentration of MCC. Generally, flow properties can be improved by forming granules of spherical shape, increasing average particle size, and the addition of glidants (20).

Carr's index is a measure of the flowability and compressibility of a powder (21). The lower the Carr's index, the better the flowability (22). Conversely, the Hausner ratio indicates the degree of densification that could result from the vibration of the feed hopper during tableting, with higher values predicting significant densification of powders while lower values are suggestive of better flowability (23). A Hausner ratio of less than 1.25 indicates good flow, values between 1.25 and 1.5 indicate poor flow that adding glidants would improve flow. However, with values greater than 1.5 even added glidants would not improve flow. The binary mixture, A50:L50 had the highest Hausner ratio and Carr's index while A75:L25 had the least values. This indicates, therefore, that A75:L25 would have a better flow than the other binary mixtures. The Hausner ratio and Carr's index values for A25:L75 was greater than that of Microcelac®, probably due to the particle shape of Microcelac®, which enabled it readily, slip past each other. Carr's index of the excipients generally indicated good flow.

Mechanical properties

The mechanical properties (tensile strength and friability) of paracetamol tablets at a relative density of 0.90, which is representative of commercial tablets, are presented in Table 2. Tensile strength is the degree by which prepared tablets can withstand pressure particularly during production and handling without chipping or laminating (24). Friability is a measure of the durability of an uncoated tablet to abrasion, which forms part of a manufacturer's specification (25).

The tensile strength of paracetamol tablets containing

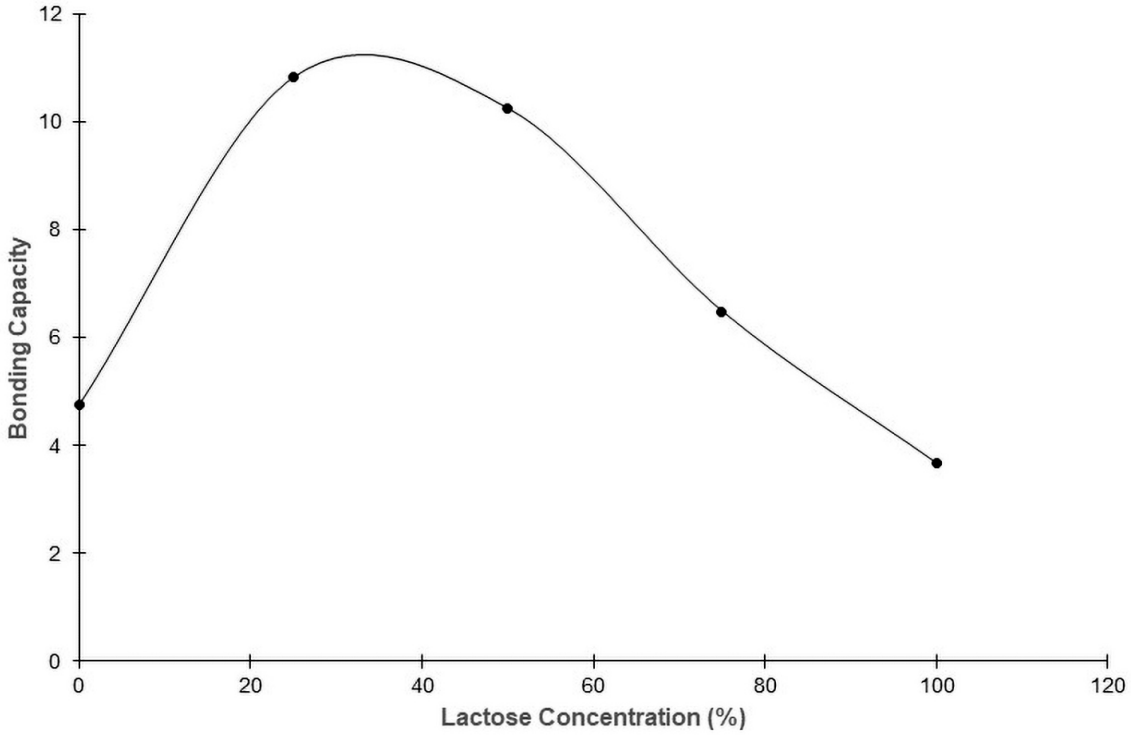

Figure 3 Plots of bonding capacity against concentration of lactose in binary mixtures of lactose and MCC.

binary mixtures increased with an increase in the concentration of MCC, while for friability decreased. The pressures employed in tableting would force the particles into a closer packing, which would increase the number of contact points, and eventually, lead to the formation of solid inter-particulate bonds (25-26). Thus, leading to the formation of tablets with greater strength that is less friable. Microcelac® had higher strength and lower friability than A25:L75. This was probably due to its smaller particle size and shape, which would enhance packing and filling of void spaces, bringing about close contact of particles and greater bonding.

The bonding capacity, κ, obtained from the Ryshkewitch-Duckworth relation (Equation 5) was plotted against the concentration of lactose contained in the binary mixtures and is presented in Figure 3. Bonding capacity of lactose appeared to have reached a maximum before the 40% concentration while the bonding capacity of MCC did not attain maximum until about 70%. This probably accounts for the tensile strength of the tablets made of A75:L25 being the tablet with the highest concentration of MCC made from binary mixtures while that of A25:L75 had the least strength. It has been shown in a previous study that bonding capacity generally correlated with tensile strength (9). The bonding capacity of Microcelac®, at porosity (Ɛ) 0.1 was 12.63, which almost doubled the value of the binary mixture A25:L75 (Table 2). thus indicating that mere mixing may not suffice in achieving the same functionality as a co-processed excipient.

Release properties

Plots of disintegration time against relative density are shown in Figure 4. The disintegration of tablets plays a vital role in the dissolution process since it determines largely the area of contact between the solid and liquid (27). Tablet disintegration time generally has been described as the net outcome of adhesive and disintegrating forces, which are activated once tablets are wetted (28). The values of disintegration time increased with increasing relative density. This could be due to the reduction in the porosity of the tablets. A

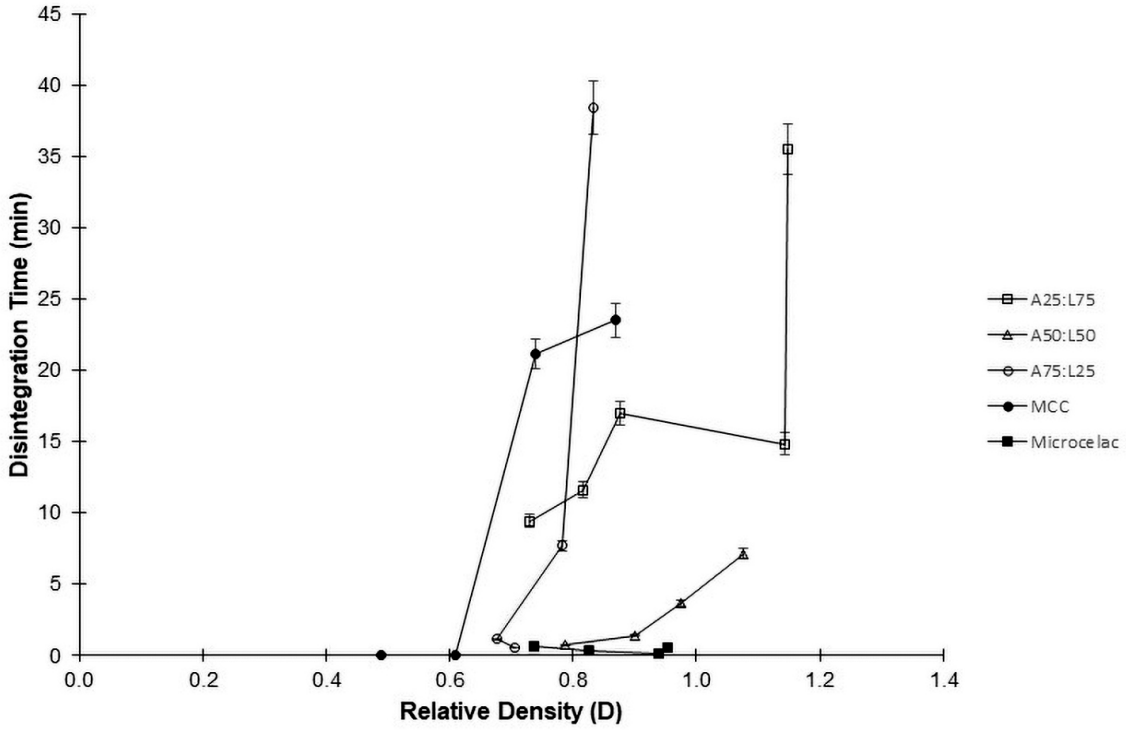

Figure 4 Plots of disintegration time against relative density of MCC, the binary mixtures and Microcelac®

decrease in porosity results in the formation of more solid bridges, thus making the destruction of the inter particulate bonds more difficult (29). Paracetamol tablets containing the Microcelac® disintegrated fastest while those containing lactose did not disintegrate within a one-hour period. The reduction in void spaces as a result of the application of pressure probably made it difficult for fluid to penetrate the pore spaces readily.

The type, concentration, and efficiency to function as a disintegrant, of the excipient used, affects the dissolution properties of the tablets. The amount of paracetamol released from the tablets was plotted against time as shown in Figure 5. The paracetamol release from tablets prepared with the binary mixture at a relative density of 0.90 increased with a decrease in lactose concentration, indicating that paracetamol tablets containing A75:L25 released a higher amount of paracetamol (Table 2). The release of paracetamol from tablets made with Microcelac® was at a faster rate than those made with A25:L75, probably due to its spray-dried nature. Spray drying has been shown to confer high solubility and in some cases bioavailability on powders (30-31). Lactose has also been shown to release drugs mainly by erosion due to its water solubility (32). The tablet containing the binary mixture, A75:L25 showed superiority in paracetamol release to both parent compounds – MCC and lactose, and the other binary mixtures. Not all tablets, however, released up to 50% or 80% of paracetamol content within 1 h. Tablets containing A50:L50, MCC, A75:L25, and Microcelac® in descending rank order released up to 50% paracetamol while only those containing A75:L25 and Microcelac®, also in descending rank order had up to 80% release within the hour.

The kinetics of drug release are presented in Table 3. The release mechanism of tablets containing lactose, A25:L75, A75:L25, MCC, and Microcelac® followed the Korsmeyer-Peppas model, while that containing A50:L50 followed the Hopfenberg model. This indicated that paracetamol release from the former was predominantly by diffusion and erosion while

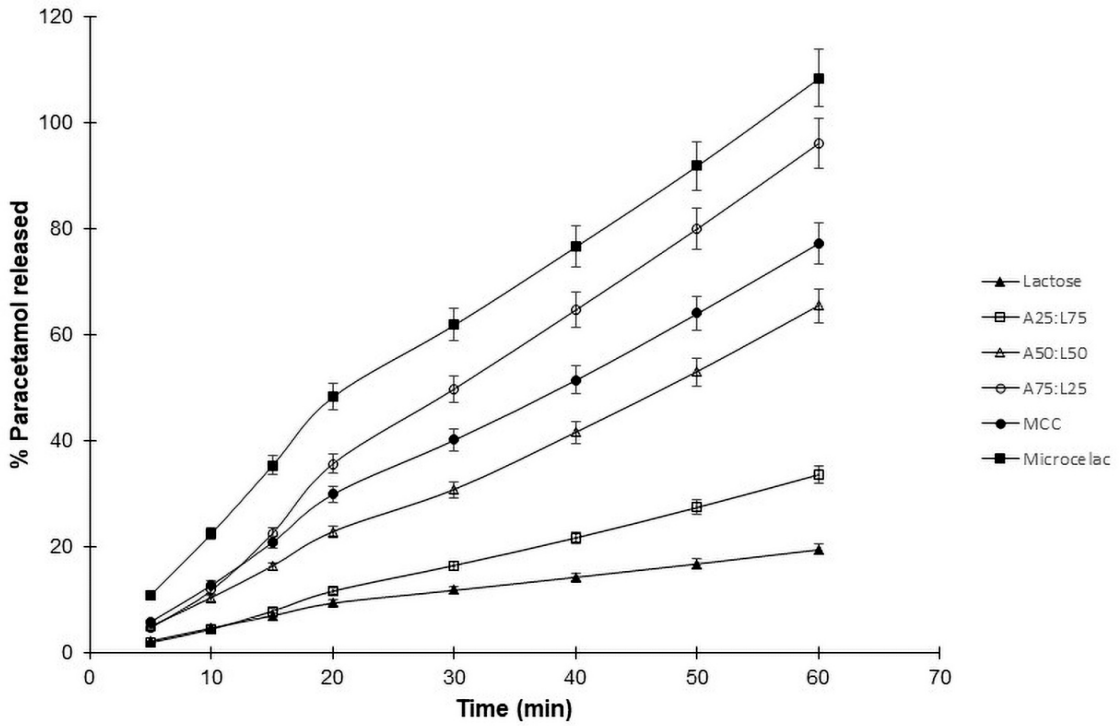

Figure 5 Plots of % paracetamol release against time of MCC, lactose, their binary mixtures and Microcelac®

the latter is released predominantly by erosion. Drug release mechanisms from tablets containing lactose, MCC, and Microcelac® were anomalous (non-Fickian) diffusion as n values fell between 0.5 and 1 but for tablets made of binary mixtures A25:L75 and A75:L25 it was Super Case II transport (relaxation) mechanism. The n value for tablets prepared from the A50:L50 mixure that followed the Hopfenberg model indicated that erosion occurred from a flat surface (33).

The release profile of the paracetamol tablets containing the different excipients was also compared using the similarity factor, f2 where values 50 – 100 indicate similarity to identical profiles. Only combinations of tablets containing lactose to those containing A25:L75 and tablets containing MCC to those containing A50:L50 were found to be comparable (Table 4).

Table 3 Values of correlation coefficient (r^2) for the various kinetic dissolution models

MODEL	LACTOSE	A25:L75	A50:L50	A75:L25	MCC	MICROCELAC®
Zero-order	0.9396	0.9969	0.9976	0.9938	0.9953	0.9712
First-order	0.9620	0.9877	0.9644	0.9127	0.9652	0.9236
Higuchi	0.9118	0.7955	0.8064	0.8007	0.8337	0.8838
Korsmeyer-Peppas	**0.9936**	**0.9977**	0.9978	**0.9939**	**0.9971**	**0.9954**
Hixson-Crowell	0.9553	0.9919	0.9800	0.9498	0.9839	0.9637
Hopfenberg	0.9620	0.9975	**0.9981**	0.9938	0.9970	0.9879

Table 4 Values of similarity factor, f_2, for various paracetamol tablets containing various excipient combinations

EXCIPIENTS IN THE PARACETAMOL TABLET	F_2
Lactose: MCC	24.41
Lactose: A25:L75	57.54
Lactose: A50:L50	30.47
Lactose: A75:L25	18.31
Lactose: Microcelac®	13.72
MCC: A25:L75	29.48
MCC: A50:L50	54.38
MCC: A75:L25	48.47
MCC: Microcelac®	33.93
Microcelac®: A25:L75	16.61
Microcelac®: A50:L50	26.85
Microcelac®: A75:L25	46.90

CONCLUSIONS

Physical mixtures of excipients did not improve the functionality of the excipients containing the binary mixtures compared to the co-processed excipients prepared by spray-drying. Both mechanical and release properties of the binary mixture of A25:L75 were much lower than that of the co-processed excipient Microcelac®, which contained the same ratio of MCC and lactose. However, the binary mixture A75:L25 exhibited the best properties for use as a directly compressible excipient in terms of its mechanical, and release properties. Thus, it could be developed commercially for use in a formulation as a directly compressible excipient.

CONFLICT OF INTEREST

The authors hereby declare no conflict of interest.

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