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Original Research Article

Effects of a co-processed novel multifunctional excipient on the tablet properties of metronidazole.

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Abstract

Purpose: The objective of this work was to formulate and determine the effects of a co-processed novel, multifunctional pharmaceutical excipient on tablet parameters of metronidazole tablets produced by direct compression.
Methods: The excipient was prepared by co-processing lactose, mucin and gelatin in a ratio of 90:1:9, dried and pulverized into powder using the co-fusion method. The excipient formulated was characterized using Differential scanning calorimetry (DSC) and Fourier transform infra-red spectroscopy (FTIR). The excipient was used to prepare metronidazole tablets and compared with other modified excipients like Cellactose® and Spray dried lactose®. Parameters evaluated on tablets include crushing strength, friability, disintegration, tablet assay and in-vitro studies.
Results: DSC analysis revealed a crystalline excipient due to the high content of lactose in the formulation while FTIR showed no interaction between the excipient and metronidazole showing compatibility. Tablets prepared had an average weight of 0.49 g, crushing strength of 4.3 KgF, friability of 0.65 %, disintegration time of 14 min and time taken for 50 % of the drug to be released was 14 min.
Conclusion: A multifunctional co-processed excipient having a filler-binder-lubricant property was prepared. The drug-excipient ratio (40:60) of the co-processed excipient gave pharmaceutically acceptable tablets that met the British Pharmacopoeia specifications as well as compared well with the modified excipients used due to improvement in the flow property as a result of co-processing.

Key words: co-processing, excipient, metronidazole, co-fusion, multifunctional.

Indexing: Index Copernicus, African Index Medicus

Introduction

The science of drug formulation dates back to ancient times, first in apothecaries and now in modern times in the pharmaceutical industries, compounding pharmacies, and research and development laboratories. The goal has always been to formulate a pharmaceutical product that is acceptable, stable, easy to administer, effective, inexpensive, and easy to formulate and that delivers the drug in a desirable way [1].
Co-processing, which means combining two or more materials by an appropriate process, could lead to the formation of excipients with superior properties compared to simple physical mixtures of their components. The main objective of co-processing is to obtain a product with added value related to the ratio of its functionality / price. The products thus formed are physically modified in such a way that they do not lose their chemical structure and stability [2]. A fixed and homogeneous distribution of the components is achieved by embedding them in mini-granules. A major limitation of mixing co-processed excipients is that the ratio of excipients in a mixture is fixed and, when developing a new formulation, a fixed ratio of excipients may not be an optimal choice for API and dose per tablet being developed. [2]

Today, the direct compression technique is one of the well accepted methods of tablet manufacturing. A wide range of materials from various sources have been developed and marketed as directly compressible diluents such as starch, polyalcohols, cellulose derivatives, lactose, inorganic substances, and sugar-based materials [3].

Co-processing has helped to develop directly compressible excipients by modifying a single substance, co-processing two or more components has also been applied to produce composite particles or co-processed excipients. Co-processed excipients are introduced to provide better tableting properties than a single substance or the physical mixture [4].

Ludipress®, a co-processed product, consists of 93.4% α-lactose monohydrate, 3.2% polyvinyl pyrrolidone® (Kollidon 30) and 3.4% crospovidone® (Kollidon CL). It consists of lactose powder coated with polyvinyl pyrrolidone and crospovidone. Although Ludipress® does contain disintegrant, the disintegration of the tablets takes longer than the tablets containing α-lactose monohydrate, Tablettose® and anhydrous β-lactose [5].

Cellactose® is a co-processed product consisting of α -lactose monohydrate (75%) and cellulose (25%). In addition to good flowability, it has good compactibility. The compactibility is attributed to a synergistic consolidation effect due to the fragmentation of lactose and the plastic deformation of cellulose. Because lactose covers cellulose fibers, moisture sorption is much less than that of microcrystalline cellulose alone. This invention relates to a process for preparing free-flowing compressible powders, and to the tableting of an active ingredient from the said powders, and more particularly, to a co-processing method to form powders and tablets that have physical and use properties that are beneficial. [6]

Direct compression is a process by which a powder mixture of an active ingredient, such as a drug, and a suitable excipient or filler, which is able to flow evenly into a die cavity, are compressed directly into an acceptable tablet. Direct compression excipients or fillers include microcrystalline cellulose, anhydrous lactose, spray dried lactose, and dicalcium phosphate [7].

The advantages of direct compression include preventing exposure of the active material to moisture and heat, and long-term physical and chemical stability due to the substantial absence of moisture or direct exposure of drug particles. The disadvantages of direct compression include the flowability requirement of powder blends, especially in high-speed tableting, limited particle bonding, and filler / binder dilution capacities [8].

One of the most frequently used fillers is lactose which is available in different forms depending upon the crystallization conditions and in various grades with different particle sizes and different compaction properties [9]. Mucin is a type of glycol-protein produced by the cells of the epithelium, or the tissue that lines the cavities and structures of the body. They are found in all types of animals and about 19 different genes have been found to code for mucins in humans with a role of producing and secreting gels into the body of the organisms [10]. Collagen is the source of gelatin and is commonly used as a gelling agent in food, pharmaceuticals, photography and cosmetic manufacturing [11]. The objective of this study was to determine the effects of a co-processed multifunctional pharmaceutical excipient on the tableting properties of metronidazole as compared to Cellactose-80® and Spray-dried lactose® as reference standards.

Materials and Methods

Materials

Lactose and gelatin (BDH Pharmaceuticals Mumbai, India) Cellactose-80 and spray-dried lactose (Ausmasco Chemicals ltd, China), metronidazole powder (BDH Pharmaceuticals, United Kingdom). All other reagents used were of analytical grade and water was double distilled.

Methods

Excipient preparation

The primary excipients were co-processed using the co-fusion method [12]. Lactose, mucin and gelatin in the ratio 90: 1: 9, were combined together by dispersing them in distilled water and heating in a water bath (Julabo – GmbH, Germany) to 40 ^{o}C. The resultant dispersion was then stirred for 15 min at the same temperature to form a paste. The resulting paste was then dried at 40 ^{o}C in a hot air oven (Gallenkamp B.S 3, England) for 2 h before screening with 1.5 mm sieve, the powder was further dried for 10 min then screened with a 500 µm sieve and stored in a screw-capped bottle over silica gel until use. The excipient so prepared was termed "Co-processed excipient" (COP).

Drug-Excipient compatibility
Fourier transform infra-red (FTIR) characterization

The FTIR analysis of the samples was carried out using Fourier transform infrared spectrophotometer (Spectrum BX, Perkin Elmer, Beaconsfield, Bucks, England).

The potassium bromide pellet method was used where 0.1 to 1.0 % sample is mixed into 200 to 250 mg fine alkali halide powder and then finely pulverized and put into a pellet forming die; metronidazole powder and components of the co-processed excipient were scanned at a range of 4000 – 1000 cm^{-1}.

Differential scanning calorimetry (DSC*)*

DSC study of the samples was conducted using DSC (Mottler Toledo, Germany). DSC cell was purged with 50 ml/min dry nitrogen. Accurately weighed samples

(2-4 mg) were heated in aluminium pans in temperature range of 25 - 250 ºC at a heating rate of 20 ºC/min. Prior to analysis, calibration of the instrument was performed using zinc (Zn) and indium (In).

Formulation of tablets

Tablets were formulated using metronidazole as the drug of choice. The co-processed excipient was used to formulate tablets by direct compression (DC) and compared with the two commercially available co-processed excipients, Cellactose – 80 and Spray-dried lactose. Each batch contained powder blends of 250 mg, 200 mg of metronidazole powder and 5 mg of magnesium stearate.
Metronidazole tablets were formulated by DC using the formula in Table 1. The different batches of the tablets were formulated by weighing appropriate quantities of metronidazole powder and the co-processed excipient or cellactose-80 or spray-dried lactose into a mixer and dry mixed for 5 min. Magnesium stearate was added as a lubricant and the mixer operated for 5 min.
A single punch tableting machine (F3, Manesty Machine Ltd., Liverpool, UK) was used at compression pressure of 5 Metric Tonnes to compress the powder mix into tablets. Before this, the die volume was adjusted to compress tablets of uniform weight by using powders weighing 500 mg. The tablets produced were then kept in air tight containers and stored in a desiccator until evaluation.

Tablet evaluation
Weight uniformity test

Twenty tablets from each batch were randomly selected and each tablet was individually weighed on an analytical balance (model 240A, PAG OERLIKON AG, Zurich, Switzerland) and the reading was recorded. The average weight of twenty tablets and standard deviation were calculated.

Table 1: Formula of prepared metronidazole tablets

Ingredients	Batch 1(mg)	Batch 2 (mg)	Batch 3 (mg)
Co-processed excipient (COP)	295	-	-
Cellactose (CEL)	-	295	-
Spray-dried lactose (SDL)	-	-	295
Metronidazole (METRO)	200	200	200
Magnesium stearate	5	5	5
Total (mg)	500	500	500

Diameter and thickness test

The Vernier caliper was used to determine the diameter and thickness of ten tablets selected randomly.

Tensile strength

The crushing strength of the tablets was measured using a tablet hardness tester (Erweka, USA). Tablet dimensions were measured. Tensile strength was calculated using equation 1 to eliminate the undesirable effect of variable tablet thickness on measured breaking force.

$$T = \frac{2F}{\pi dt} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (1)$$

Where T is the tensile strength (MN/m^2), F is the observed breaking force (N), d is the diameter (mm) and t is the thickness of the compact (mm).
lowest position the wire mesh was at least 25 mm above the bottom of the beaker. One tablet was placed into each of the tubes. The apparatus was operated for specified time and temperature at 37 ± 2 °C. Time for complete disintegration of tablet was noted.

Friability

This was determined using a Roche friabilator as described in the USP/NF 2009[13]. Ten tablets were weighed (X) and transferred to the friability test apparatus at 25 rpm for 4 min. The tablets were removed, de-dusted and re-weighed (Y).
Friability was calculated by using equation 2:

$$\% \text{ Friability} = \frac{X - Y}{X} \text{ x } 100 \dots\dots (2)$$

Disintegration test

The disintegration apparatus (Erweka, Germany) was suspended in a 1000 mL beaker containing distilled water. The volume of liquid was taken such that when the apparatus was in highest position the wire mesh was at least 25 mm below the surface of the liquid while when the apparatus was in lowest position the wire mesh was at least 25 mm above the bottom of the beaker. One tablet was placed into each of the tubes. The apparatus was operated for specified time and temperature at 37 ± 2 °C. Time for complete disintegration of tablet was noted.

In-vitro Drug Release Studies

The dissolution profiles of metronidazole tablets were determined using the USP XXVIII basket method for the various batches of the tablets.
A dissolution medium of 900 mL of 0.1 M HCL solution for metronidazole maintained at (37 ± 0.5) ºC with a basket revolution of 50 r/min was used [13]. A 5 mL volume of leaching fluid was withdrawn at pre-determined time intervals (5, 10, 20, 30, 45 and 60 min) and replaced with an equivalent volume of the dissolution medium after each withdrawal.

The withdrawn samples were filtered and diluted with an equal volume of 0.1 M HCL solution. This was continued for 60 min. The absorbance of the resulting solutions was measured spectrophotometrically at λ max 277 nm for metronidazole. The percentage of drug released at each interval was determined using the standard calibration plot obtained for the pure drug.

Data analysis

All data obtained were expressed as mean ± SD.
Statistical analysis was performed with one-way analysis of variance (ANOVA) comparison test of Graphpad prism 6. A confidence level of 95 % ($\rho < 0.05$) was considered satisfactory for determining significant differences.

Results

FTIR

The FTIR spectrum of pure metronidazole powder showed characteristic peaks at 3101 cm^{-1}, [1], and 3206 cm^{-1}. These peaks observed for metronidazole remained unchanged when compared with the spectral data of the combination (Figure 1).

DSC

The DSC thermogram of metronidazole (METRO) revealed a single sharp peak, while that of COP revealed double peaks (Figure 2). The DSC thermogram of COP showed a strong dehydration endotherm with an onset temperature of 176 ^{O}C and a peak maximum temperature of 182 ^{O}C. The combination of METRO and COP showed the compatibility of METRO with COP as all the characteristic peaks were represented. The overlay of the two thermograms for COP and PM (Physical mix) showed a similarity in their endothermic peaks but for some slight difference showing compatibility and no serious change or formation of a new compound as a result of co-processing

Tablet parameters

Table 2 shows some parameters of the metronidazole tablets formulated. Tablets from all the batches gave mean crushing strength values between 4.0 and 7.3 KgF. Friability values ranged between 0.65 and 0.86% while disintegration time was less than 6 min for batches II and III, and less than 15 min for batch I. Less than 15 min is considered to be the least disintegration time for conventional tablets [14].
The release profiles of the various batches of metronidazole at T 50% was less than 8 min and less than 23 min at $T_{90\%}$ as seen in figure 4. There was no significant difference in the release rates of the three excipients at a ρ value < 0.05.

Discussion

The use of differential scanning calorimetry (DSC) in a wide range of pharmaceutical applications ranging from the characterization of materials to the evaluation of drug-excipient interactions via the appearance, shift, or disappearance of endothermic or exothermic peaks has been employed [15]. DSC has equally been used to investigate drug-excipient compatibility and thermal stability [16]. From the DSC result obtained, this goes a long way to show that co-processing or particle manipulation did not in any way result in the formation of a new compound and this is comparable to the work of Gramaglia *et al.*, 2015 [17].

The FTIR spectra as well as the DSC ruled out the possibility of chemical interaction and complex formation between metronidazole and the co-processed excipient during the mixing process. Crushing strength values greater than or equal to 4 KgF is considered to be the minimum for conventional tablets [18]. Tensile strength and hardness serve as the indicators of the strength of compact. pharmaceutical ingredients which bond well together are capable of forming tablets with high tensile strength. The tensile strength of tablets prepared with different excipients ranked in the following order: CEL > COP > SDL with CEL exhibiting superior tensile strength when compressed at the same pressure for metronidazole. This is attributed to the high bonding capacity it possesses due to the synergistic effect of consolidation by fragmentation of lactose and plastic deformation of cellulose [19].

Tablet friability is a measure of the ability of tablets to withstand stress. According to the USP/NF 2009[13], tablets should show no more than 1% loss in weight. This test is more rigorous than the crushing strength test since in the friability test, compacts are subjected to mechanical stresses simulating wearing due to handling and mechanical shock. All the batches of tablets produced met the requirement. The statistics showed that at a ρ value < 0.05, $R^2 = 0.9829$, there was significant difference between their friability values. This is so because all the batches are made up of different excipients co-processed together though they all contain the parent material lactose. The crushing strength of a tablet can highly affect the release rate of a drug [20]. Usually, when there is an increase in crushing strength of a tablet, it is accompanied by a decrease in the release rate, as a result of a decrease in tablet porosity [21]. Although this depends on the ingredients involved in co-processing like in the case of CEL which contains cellulose and lactose, but for COP having a crushing strength of 4.3 KgF, it took 4 min to release 50% of the drug as against 4.0 KgF and 7 min for SDL.

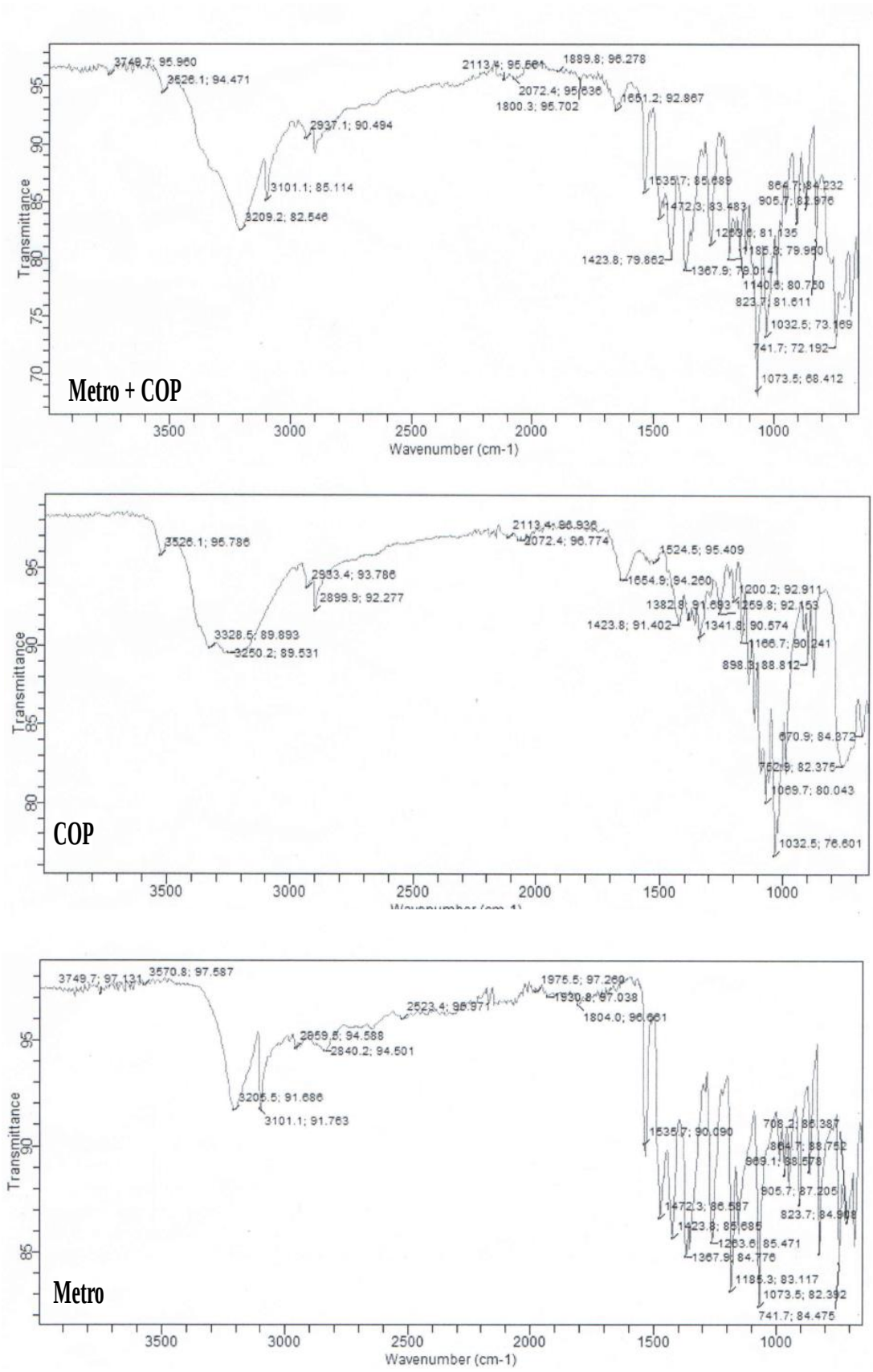

Figure 1: FT – IR Overlay spectra of METRO + COP, COP and METRO

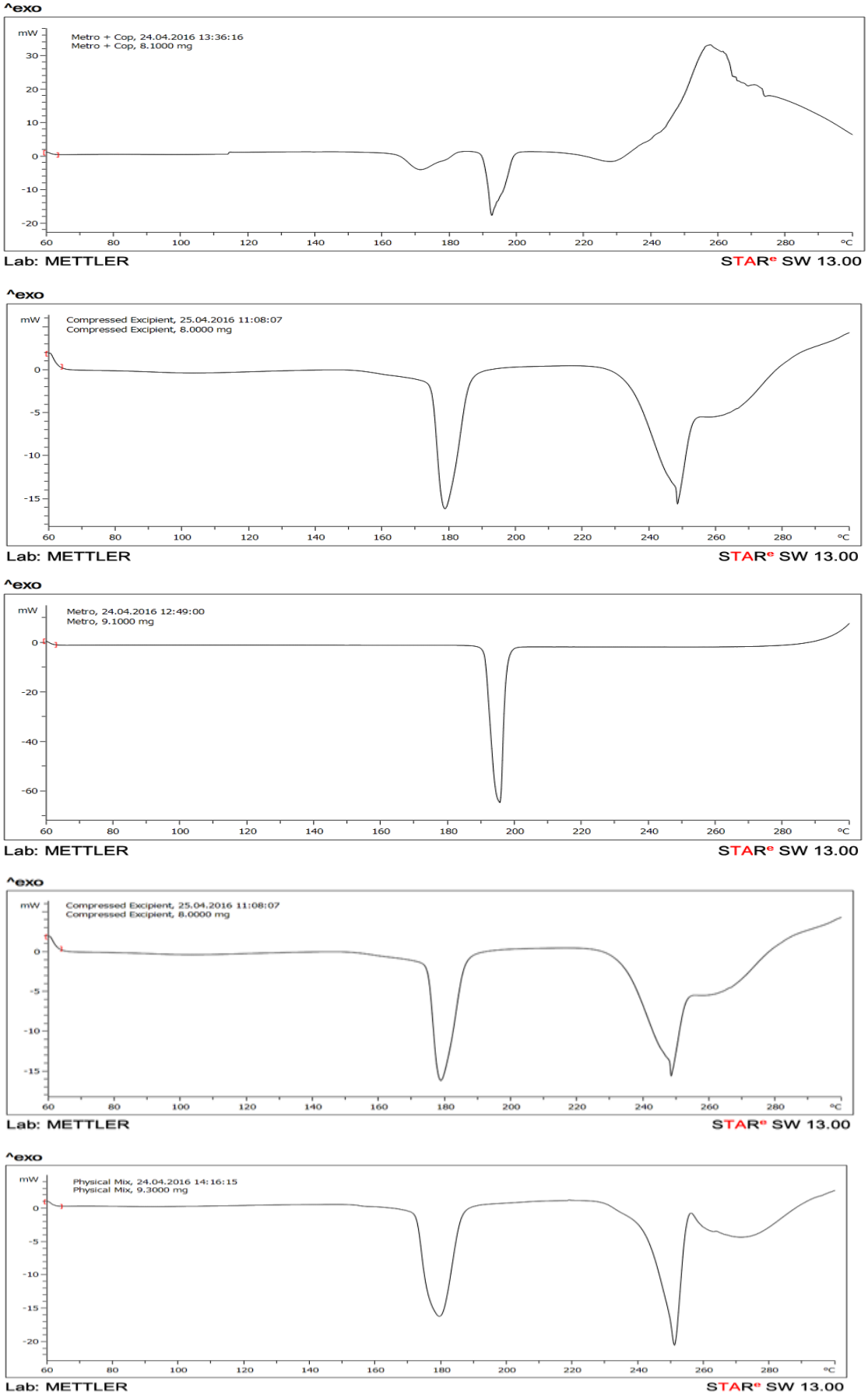

Figure 3: DSC Plots of COP and Physical mix

Table 2: Properties of formulated metronidazole tablets

	Metronidazole Parameters					
Batch	CS (KgF)	TS (MN/m^2)	FR (%)	DT (min)	$T_{50\%}$ (min)	$T_{90\%}$ (min)
I	4.3 (0.51)	0.58	0.65	14 (0.02)	4	12
II	7.3 (1.03)	1.01	0.68	2 (0.0)	1	1
III	4.0 (1.4)	0.52	0.86	5(2.1)	7	22

KEY: Batch I: COP formulation, Batch II: CEL formulation, Batch III: SDL formulation, CS: Crushing strength, TS: Tensile strength, FR: Friability, DT: Disintegration time, $T_{50\%}$: Time taken for 50 % of the drug to dissolve, $T_{90\%}$: Time taken for 90 % of the drug to dissolve.

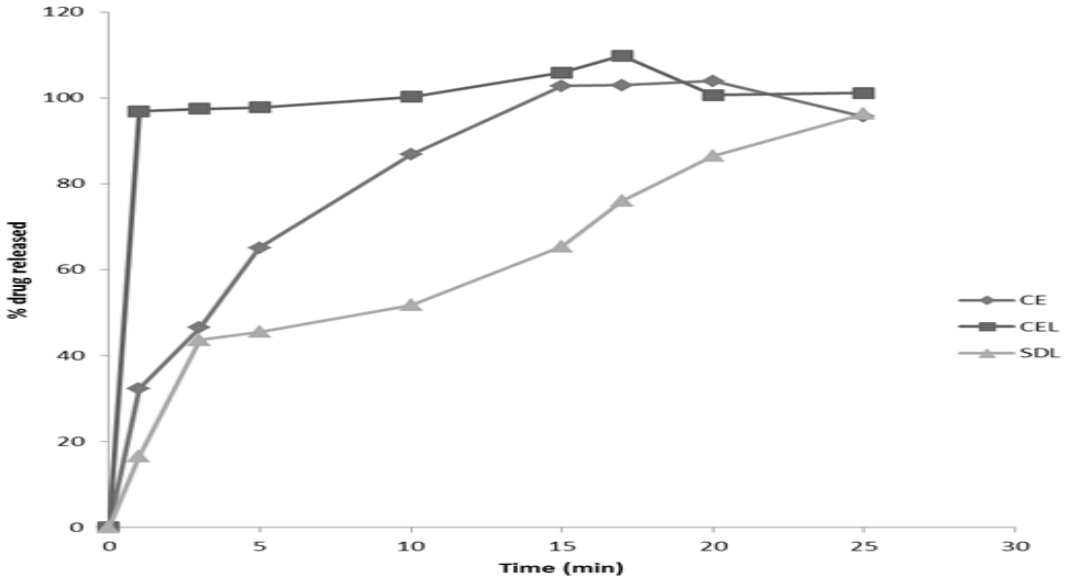

Figure 4: Percentage of metronidazole released from different tablet formulations.

Disintegration tests are only indirectly related to drug bioavailability and product performance. For conventional immediate release tablets,

disintegration should not exceed 15 min. It is markedly affected by formulation ingredients and processing, hence, it's used as a quality control tool. The study revealed that all the tablets produced passed the disintegration test with CEL and SDL tablets disintegrating within 8 min. This has been attributed to the capillary action of cellulose (present in Cellactose) in contact with water as well as its water sorption capacity. This agrees with the works done by ElShaer *et al.,* 2013[22] and Keny *et al.,* 2010 [23]. The longer disintegration time exhibited by COP can be attributed to the presence of mucin in the co-processed excipient, when in contact with water forms a viscous gel which retards disintegration [24].

The intrinsic properties of the drug, its size and components of its formulation especially thickeners can affect the dissolution of a drug [25]. All the batches met the [26] specification which states that 70 % of the uncoated tablet is expected to dissolve within 40 min. Another important parameter from the release studies is the $T_{50\%}$ value which is very critical in formulating drugs that may be needed for fast onset of action. This indicates the time at which 50% of the drug was dissolved, which means that in less than 8 min, 50% of the drug from all batches was already available for absorption. In formulating drugs for which a fast onset of action is desired, the $T_{50\%}$ value may find its usefulness.

Conclusion

The co-processed excipient (COP) was used in formulating pharmaceutically acceptable tablets that met the BP specifications and compared well with the reference standard co-processed excipients (Cellactose® and Spray-dried lactose®) already in the market. Therefore, it may be a better alternative as an excipient in fast release of metronidazole tablets.

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Conflict of interest

We declare that we have no conflict of interest.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors". Mohammed conceived the study, Isah, Allagh and Builders, designed the study and Mohammed collected and analyzed the data.

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