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RESEARCH ARTICLE

Comparative study of pharmaceutical properties of some new derivatives of sulfamethoxazole

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Abstract

This paper reports the changes in various physical properties associated with the derivatization of sulfamethoxazole. The properties studied include moisture content, crystallanity, particle size distribution, porosity, flow, compressibility and compactability. It was found that the derivatives, salicylidene-sulfamethoxazole-Zn(II) • H_2O and salicylidene-sulfamethoxazole-Cu(II) • H_2O are crystalline substances. The moisture content was found to be highest in salicylidene-sulfamethoxazole-Zn(II) • H_2O followed by salicylidene-sulfamethoxazole-Cu(II) • H_2O and sulfamethoxazole. The copper complex contained only chemically bonded water, whereas the zinc complex contained both bonded and absorbed water, which affected the strength of the tablets prepared from the three materials accordingly. The particle size decreased on derivatization and complexation with metal ions and the trend was: sulfamethoxazole > salicylidene-sulfamethoxazole-Cu(II) • H_2O > salicylidene-sulfamethoxazole-Zn(II) • H_2O. This trend was represented by better compactability shown by salicylidene-sulfamethoxazole-Cu(II) • H_2O and salicylidene-sulfamethoxazole-Zn(II) • H_2O as compared with sulfamethoxazole. Salicylidene-sulfamethoxazole-Zn(II) • H_2O had the highest porosity followed by salicylidene-sulfamethoxazole-Cu(II) • H_2O, and sulfamethoxazole; this resulted in better compressibility behavior of the complexes. Thus it was observed that salicylidene-sulfamethoxazole-Cu(II) • H_2O and salicylidene-sulfamethoxazole-Zn(II) • H_2O formed stronger compacts. The values of angle of repose and flow rate show better flow properties for salicylidene-sulfamethoxazole-Cu(II) • H_2O as compared with sulfamethoxazole and salicylidene-sulfamethoxazole-Zn(II) • H_2O. It was concluded that derivatization substantially changed the pharmaceutical properties, which have important role to play in formulation of solid dosage form.

Keywords: *Pharmaceutical properties; compression properties; sulfamethoxazole derivatives; metal complexes; metal-based drugs*

Abbreviations: PXRD, Powder X-ray diffraction; Dv, size of the particle in μm based on the volume v of the particle; SG, specific gravity; ε, porosity; ρ, density; CI, Carr's Index; HR, Hausner ratio; α, angle of repose; P_y, deformation pressure; SMZ, Sulfamethoxazole; Sal-SMZ-Zn, salicylidene-sulfamethoxazole-Zn(II)• H_2O; Sal-SMZ-Cu, salicylidene-sulfamethoxazole-Cu(II) • H_2O.

Introduction

Sulfamethoxazole (SMZ) is a sulfonamide bacteriostatic antibiotic. It is widely used in a synergistic combination with trimethoprim, commonly known as co-trimoxazole. It is active against *Escherichia coli*, *Haemophilus influenzae*, *Staphylococcus aureus*, and some anaerobes. There are several side-effects, the most common being the gastrointestinal disorder. The wider use of antibiotics in humans and animals and in areas other than the treatment and prophylaxis of disease have resulted in a serious problem of drug resistance. Various strategies have been worked out and tried to cope with the resistance problem and enhance the activity, or broaden the spectrum of drugs.[1] Preparation of different synthetic derivatives of antibacterials based on structure-activity relationship has been one of the best approaches. The prevalence of strains resistant to trimethoprim-sulfamethoxazole is increasing in many communities.[2] This is of concern as this combination is considered as the first-line therapy for uncomplicated

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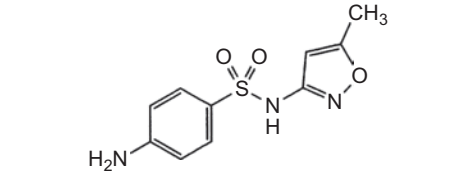
urinary tract infections.[3] In an effort to find a better sulfonamide, medicinal chemists have reported some new derivatives of SMZ including the Schiff base derived from salicylaldehyde.[4,5] Several metal complexes of SMZ[6] and its derivatives have been reported in literature and it has been shown that the metal-Schiff-base complexes of some antibiotics possess good potential as more effective and safe drugs.[7] Our work regarding the synthesis and biological evaluation of salicylidene-sulfamethoxazole-Zn(II) • H_2O (Sal-SMZ-Zn) and salicylidene-sulfamethoxazole-Cu(II) • H_2O (Sal-SMZ-Cu) (Figure 1) has demonstrated clear benefits of these derivatives over the parent drug SMZ.[5] We thought it worthwhile to study the conversion of these derivatives into tablets, one of the most convenient dosage forms, and develop them as drug candidates for clinical studies. Therefore, the present work was carried out to investigate the suitability of these synthetic materials for preparation of tablets. The parameters which matter in tableting of powders, including crystallanity, moisture content, particle size, densities, porosity, flow, compressibility and compactibility, were investigated and a comparison of these properties of the new derivatives with those of SMZ is presented here.

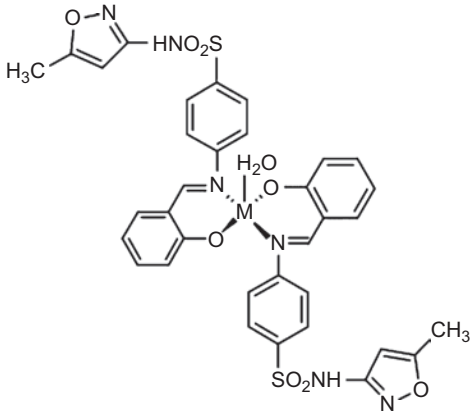
Experimental

Materials

SMZ (BP, Lot # SMZ-0213, Askari Pharmaceuticals, Pakistan), zinc acetate dihydrate (Extrapure, E. Merck, Germany; Lot #351A 804400), potassium hydroxide (Extrapure, E. Merck, Germany; Lot #B634632 431), salicylaldehyde (Extrapure, E. Merck, Germany; Lot #S5091440 844), methanol (Extrapure, E. Merck, Germany; Lot #012 K137691089), and copper acetate monohydrate (BDH, UK; Lot #K24338356 825) were used without further purification.



Sulfamethoxazole



Salicylidene-sulfamethoxazole-M • H_2O
M = Cu (II), Zn (II)

Figure 1. Structures of the compounds under investigation.

Methods

Preparation of Schiff base metal complexes

The complexes were prepared as per method developed earlier.[5] SMZ (0.507 g, 2 mmol), salicyaldehyde (0.209 g, 2 mmol) and $Cu(CH_3COO)_2.H_2O$ (0.200 g, 1 mmol) or $Zn(CH_3COO)_2.2H_2O$ (0.220 g, 1 mmol) were dissolved in methanol (25 mL) separately, the pH was adjusted to 7–8 by use of KOH (0.1% in methanol), and the mixture was refluxed for 2–3 h. The product was isolated after reduction of volume by evaporation. It was filtered off, washed with methanol and dried under vacuum. Yield: Sal-SMZ-Zn 80%; Sal-SMZ-Cu 85%.

Powder X-ray diffractometry

Powder X-ray diffraction (PXRD) measurements were carried out over a range of 5–50° (2θ) in steps of 0.020° on a diffractometer (D/MAX-II, Rigaku, Japan) equipped with monochromatic X-rays.

Moisture content

This was determined at room temperature on 799 GPT Titrino (Metrohm, Switzerland), an automatic Karl-Fischer titrator, using accurately weighed amount of the powder (approx. 300 mg), pyridine-free reagent and methanol as solvent. The Karl-Fischer method measures coordinated and lattice water alike.[8]

Particle size distribution

This was determined by particle-in-liquid method using laser diffractometer (Mastersizer 2000, Malvern Instruments Ltd, UK). A slurry was prepared by dispersing the powder (2 g) in ethanol-water (50:50, 20 mL) mixture. The slurry was sonicated to dissociate the agglomerates. Approximately 5 mL of slurry was used for each measurement. Particle size distribution was determined as a span, which is a measure of width of the size distribution. The narrower the distribution, the smaller the span becomes. The span was calculated using the equation: Span = [D(ν, 0.9) – D(ν, 0.1) / D(ν, 0.5). The particle size was determined as the mean of three measurements. Results were expressed as D(ν, 0.1), D (ν, 0.5), and D (ν, 0.9), where D is the size of the particle in μm based on the volume, ν, of the particle, and 0.1, 0.5, 0.9 indicate the percentage, i.e. 10, 50, 90% respectively, of the particles.

True density

This was determined by the specific gravity bottle method using 0.5 g of the powder in xylene. The true density, (ρ_{true}), was calculated using equation $\rho_{true} = w / SG\,[(a+w) - b]$[9,10] where, w is the weight of powder, SG the specific gravity of xylene, a is weight of the bottle filled with xylene and b is weight of bottle filled with the powder and xylene. The determination was performed in triplicate and reported as the mean.

Bulk and tap densities

The powder (10.00 g) was transferred to a 50 mL clean and dry graduated cylinder. The cylinder was lightly tapped twice to collect all the powder sticking to the walls of the cylinder. The volume, V_0 was then read directly from the cylinder. The cylinder was then tapped 500 times using tap density analyser (Vanderkamp Model 10703, Vankel, USA) and the volume V_{500} was determined according to the method given in British Pharmacopeia 2007. The bulk and tapped densities were calculated as the ratio of the weight to volume (V_0 and V_{500} separately).[11]

Porosity

Porosity of test powders was calculated using the equation $\varepsilon = (1 - \rho_{tap} / \rho_{true}) \times 100$ where ε, ρ_{tap} and ρ_{true} are porosity, tap density, and true density, respectively. Carr's Index and Hausner ratio: Carr's Index (CI)[12,13] and Hausner ratio (HR)[13,14] were calculated using the equations: $CI = [\rho_{tap} - \rho_{bulk}) / \rho_{tap}] \times 100 = [(V_0 - V_f) / V_0] \times 100$; $HR = \rho_{tap} / \rho_{bulk} = V_0 / V_f$. Where V_0 and V_f are initial and final volumes.

Flowability

The flowability was determined by two methods and the results were reported in terms of angle of repose (α) and flow rate (g s^{-1}). These parameters were determined by using the flow meter (Powder Analyzer Type PTG, Pharma Test, Hainburg, Germany) according to the USP method by using 10 g of the sample.[13] All the measurements were made in triplicate.

Compact preparation and evaluation

Compacts, weighing about 300 mg, were prepared on a hand-operated hydraulic press (Schimadzu, Japan) at different compression pressures ranging from 6–60 MPa using a 13-mm die, flat-faced punches, and a dwell time of 30 s. Before each compression, the die and the punches were lubricated with a dispersion of magnesium stearate in ethanol (1% m/v). After ejection, each compact was weighed accurately and its dimensions (thickness and diameter) were determined by use of a screw gauge micrometer that had a 0–25 mm scale and was capable of differentiating up to 0.01 mm. The tablet thickness was noted as the average of 5 measurements made at five different points between the two surfaces of the compact. This information was used for calculation of relative density using the relationship $\rho = \rho_{app} / \rho_{true}$, which is essential parameter for Heckel analysis, where ρ_{app} is the apparent density of the compact at a particular pressure and ρ_{true} is the true density of the powder. The compacts were stored over silica gel in a desiccator for 24 h to allow for hardening.[15]

Hardness

The hardness of the compacts was determined by using an automatic hardness tester (TBH250 TD Erweka, Germany) after 24 h.

Heckel analysis

The porosity of the compacts was calculated using the relationship $\varepsilon = 1 - \rho_{app\rho} / \rho_{true}$, where ε is the porosity of the compacts, ρ_{app} is the apparent density of the compact, and ρ_{true} is the true density of the particles. The ratio of $\rho_{app\rho} / \rho_{true}$ is a measure of the relative density of the compact. The ρ_{app} was calculated from the ratio of the tablet mass to the volume of the compact ($v = \pi r^2 h$, where r is the radius and h the thickness of the compact). The Heckel plots[16] were constructed by plotting the log natural (ln) of the inverse of the compact porosity against the respective compression pressures. Regression analysis was performed on the linear portion of the curve, and the slope obtained was converted to mean deformation pressure (P_y) using the relationship: $P_y = 1/\text{slope}$. The statistical analysis was performed by use of Statgraphics® Plus software.

Results and discussion

The derivatives of SMZ were easily obtained and characterized as per reported methods.[4,5] The results of the various measurements are given in Tables 1–3 and Figures 2–6, and are discussed as follows.

Moisture content

The moisture content (coordinated plus adsorbed water) of the materials is given in Table 1. Sal-SMZ-Zn

Table 1. Powder properties.

Parameter	SMZ	Sal-SMZ-Cu	Sal-SMZ-Zn
Moisture (% w/w)	0.25 ± 0.01	1.16 ± 0.02	7.00 ± 0.02
ρ_{true} (g mL^{-1})	1.69 ± 0.05	1.76 ± 0.03	1.55 ± 0.04
ρ_{bulk} (g mL^{-1})	0.48 ± 0.01	0.37 ± 0.01	0.32 ± 0.01
ρ_{tap} (g mL^{-1})	0.67 ± 0.01	0.55 ± 0.01	0.52 ± 0.00
Bukliness (mL g^{-1})	2.10 ± 0.02	2.70 ± 0.01	3.12 ± 0.01
ε (%)	60.94 ± 0.08	68.75 ± 0.06	66.45 ± 0.06
HR	1.40 ± 0.01	1.48 ± 0.01	1.62 ± 0.01
CI (%)	28.78 ± 0.03	32.72 ± 0.05	38.78 ± 0.05
α(10 g, i.d. 10 mm, 20 rpm)	32°	27°	34°
Flow rate (g s^{-1})	0.409	0.461	0.207

Table 2. Particle size analysis data.

Compound	Particle Size (μm) D(ν,0.1)	D(ν,0. 5)	D(ν,0. 9)	Particle size distribution, span (μm)	Specific surface area ($m^2 g^{-1}$)
SMZ	10. 6±0.1	37. 7±0.2	81. 2±0.3	1. 8	0. 49±0.01
Sal-SMZ-Cu	5.7±0.01	29.7±0.1	62.9±0.2	1.9	0.68±0.01
Sal-SMZ-Zn	0.7±0.01	3.1±0.01	10.4±0.1	3.1	3.18±0.01

Table 3. Heckel analysis data.

Product	Compression pressure range (MPa)	R^2	Slope	P_y (MPa)
SMZ	6–10	0.993	0.0195	51±0.02
Sal-SMZ-Cu	6–16	0.963	0.0158	63±0.01
Sal-SMZ-Zn	6–14	0.984	0.0428	23±0.01

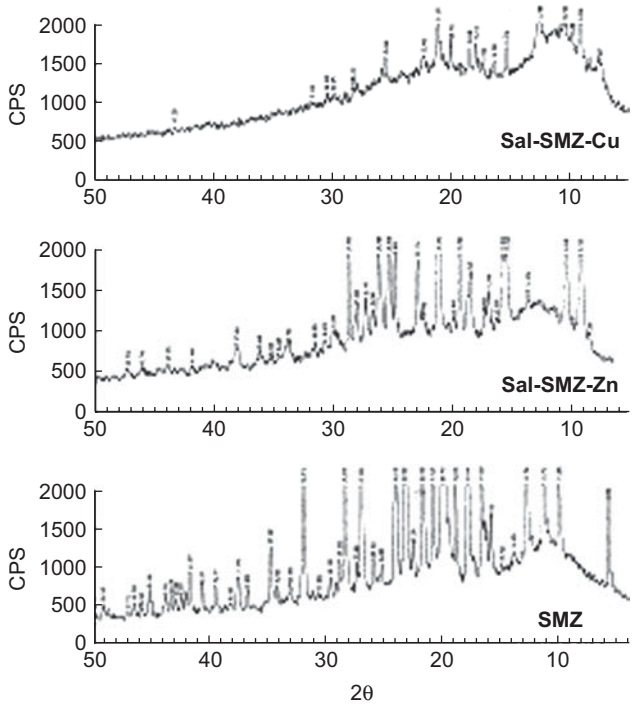


Figure 2. PXRD spectra.

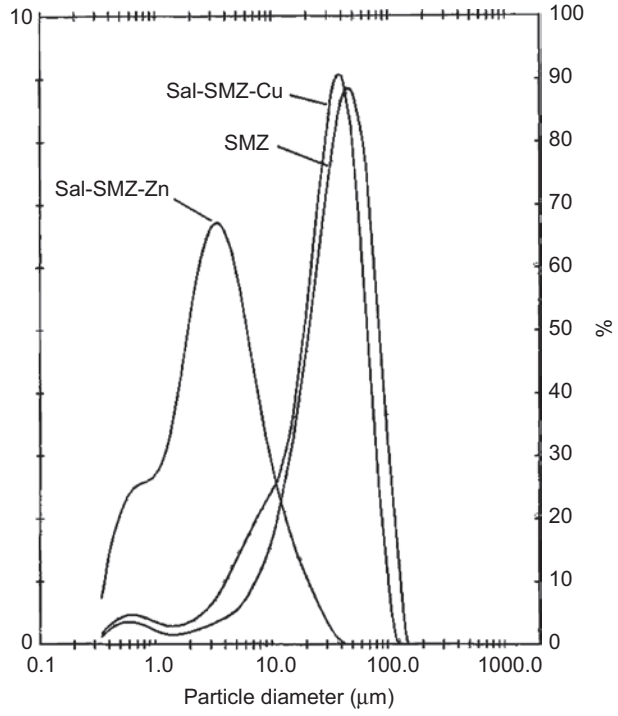


Figure 3. Particle size distributions.

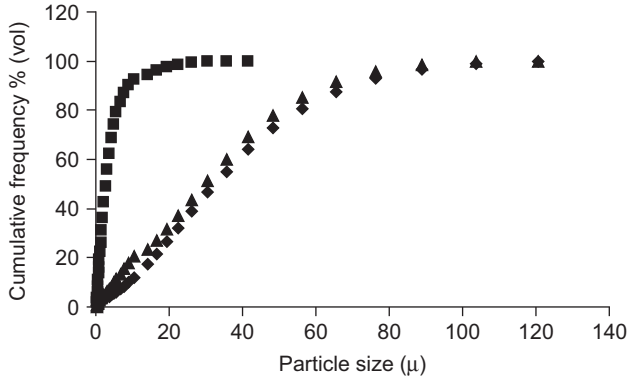


Figure 4. Comparison of cumulative frequency (volume) of smz (◆), sal-smz-Zn.H_2O (■), and sal-smz-Cu.H_2O (▲).

exhibited the highest moisture content followed by Sal-SMZ-Cu and SMZ. As far as the nature of the moisture content is concerned it is chemically bound (through coordinate covalent bond) water in case of Sal-SMZ-Cu, while in case of Sal-SMZ-Zn it is in form of bound as well as lattice water as characterized by thermogravimetric and spectroscopic techniques and reported earlier.[5] Moisture content is known to have significant effect on physico-mechanical properties, which play role in tableting process.[17,18] The presence of free moisture on particle surface helps in reduction of friction between the particles leading to increased fluidity, reduction in tablet porosity and increase in fracture resistance.[18,19] On the other hand, adsorbed water also lowers surface energy of crystals and enhances adhesion with the matrix as well as the die surfaces of the compression machine, which may also result in lower tablet strength.[20] As the water content of the new derivative Sal-SMZ-Cu is part of the molecule (forming coordinate covalent bond with the metal atom), it does not pose a threat to the quality and nature of the material itself, however it may be helpful in compression process by providing cohesion among the particles. However, in the case of Sal-SMZ-Zn both

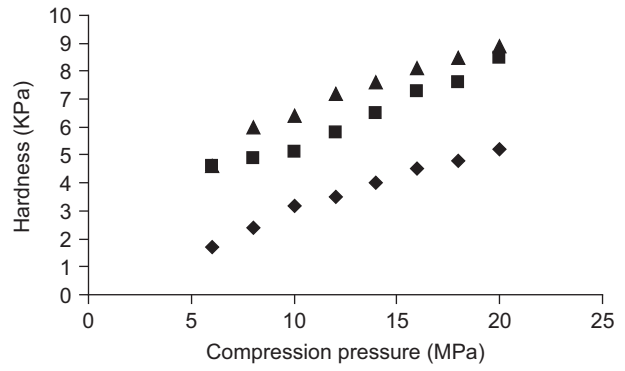


Figure 5. Comparison of hardness of smz (◆), sal-smz-Zn.H_2O (■), and sal-smz-Cu.H_2O (▲).

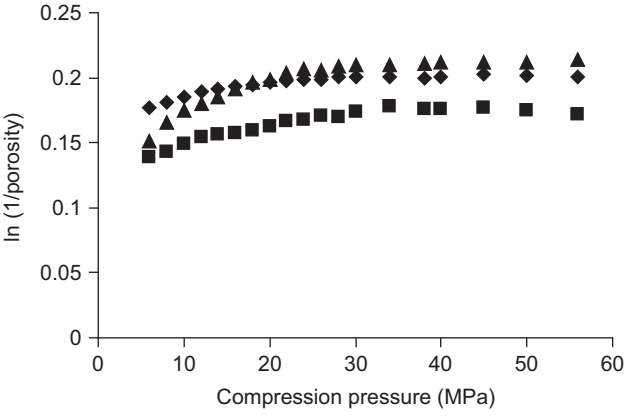


Figure 6. Comparison of Heckel plots of smz (◆), sal-smz-Zn.H_2O (■) and sal-smz-Cu.H_2O (▲).

the types of water are present suggesting lower tablet strength, which is substantiated by the results obtained in this study as shown in Figure 5.

Crystallanity

The powder X-ray diffractograms of SMZ and its derivatives are shown in Figure 2. All the three materials exhibit crystalline character. It is generally understood that crystalline materials exhibit high elasticity and brittleness when subjected to mechanical stress;[21] therefore, it may be considered appropriate to introduce amorphous character by milling the materials under investigation before granulation and compression into tablets.

Particle size distribution

The results of particle size analysis are presented in Table 2 and Figures 3 and 4. Figure 3 shows the cumulative particle size distribution. It appears that the particle size distribution of SMZ and Sal-SMZ-Cu is almost comparable, whereas Sal-SMZ-Zn differs markedly as compared with that of SMZ (Table 2, Figure 4). Cumulative size range showed narrow and comparable span for SMZ and Sal-SMZ-Cu, whereas Sal-SMZ-Zn had a wider span (Table 2). The particle size trend was found to be: SMZ > Sal-SMZ-Cu > Sal-SMZ-Zn. This trend is substantiated by better compactability shown by Sal-SMZ-Cu and Sal-SMZ-Zn as compared with SMZ (Figure 5).

Density

The bulk, tap, and true densities for the powders are listed in Table 1. SMZ has the highest bulk and tap densities, followed by Sal-SMZ-Cu, and Sal-SMZ-Zn. The increase in true density of Sal-SMZ-Cu would present benefits in tablet formulation as it has been observed that most of the active pharmaceutical ingredients need to be densified before tableting so that a sufficient dose can be administered in a reasonably sized dosage form.[22]

Bulkiness

The bulkiness, also known as specific bulk volume, is defined as the reciprocal of bulk density.[23] The order of bulkiness was found to be: Sal-SMZ-Zn > Sal-SMZ-Cu > SMZ (Table 1). Thus the complexes would require lesser quantities of bulking agents required for formulation and however a voluminous packaging will be required.

Porosity

Sal-SMZ-Cu showed the highest value for porosity followed by Sal-SMZ-Zn, and SMZ (Table 1). This shows that porosity has increased slightly on formation of Schiff base metal complexes suggesting that the new materials will exhibit better compressibility[22] which is supported by the Carr's compressibility index values which are higher than that of SMZ (Table 1).

Flow

The flow is typically determined by powder properties such as density, surface area, moisture content, particle shape, particle size, and size distribution.[24,25] The angle of repose, Hausner ratio and Carr's index are considered as indirect measure of powder flowability.[26] These parameters are listed in Table 1. These values are consistent with the flow rates determined by flow meter (Table 1). The values of angle of repose and flow rate in case of Sal-SMZ-Cu indicate an improvement in flowability as compared with SMZ.

Hardness

The relationship between hardness of the compacts and the applied pressure is shown in Figure 5. These results

clearly show formation of stronger compacts by Sal-SMZ-Cu and Sal-SMZ-Zn.

Heckel analysis

Heckel analysis was performed to study the effect of applied pressure on the changes in relative density of the powder bed during compaction.[27] The Heckel plots for SMZ, Sal-SMZ-Cu, and Sal-SMZ-Zn are shown in Figure 6. The results of the analysis are listed in Table 3. The trend of the slopes of the Hekel plot was found to be Sal-SMZ-Zn > SMZ > Sal-SMZ-Cu which indicates that plasticity/ductility improved markedly in case of Sal-SMZ-Zn and deteriorated in case of Sal-SMZ-Cu.[16,28,29]

Conclusion

The data presented in this study indicates better overall tableting properties, such as porosity, compactability and densities, for the new derivatives under investigation as compared with those of the parent drug SMZ.

Declaration of interest

There is no conflict of interest involved in this study.

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