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Effect of Polyethylene Glycol and Sodium Lauryl Sulphate on the Compaction Characteristics of Eudragit and Drug Release from its Matrix

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Abstract: A study on the compaction characteristics of Eudragit l-100 both in the presence and in the absence of two commonly used additives, polyethylene glycol 6000 (PEG 6000) and Sodium Lauryl Sulphate (SLS) was done. Eudragit granules, with and without the additives and drug were prepared separately by the wet granulation method and compacts were made at varying compression pressures. Compaction characteristics using Kawakita and Heckel analysis revealed a concentration dependent effect of the additives on the compressibility of Eudragit granules, with 2.5% PEG 6000 producing the largest effect and 5.0% PEG 6000, the least. Irrespective of the concentration of PEG 6000, the yield value increased, while SLS either had no effect or decreased the yield value of Eudragit granules. The highest yield value of 21.69 kN was produced by formulations containing 2.5% PEG 6000. While in some cases, the effect of the additive was slight, in others, it was drastic. The extent and nature of the effect depended on both the type and concentration of the additive used. SLS was found to increase the deformation of Eudragit more than PEG 6000. *In vitro* dissolution in simulated intestinal fluid as indicated by time for 70% drug release ($t_{70\%}$) shows that both additives modulated drug release, with 2.5 % SLS and 5% PEG 6000 enhancing drug release, while 5% SLS resulted in retarded but erratic drug release. The results of this study show that additives such as PEG 6000 and SLS affect the compaction characteristics of Eudragit l-100 and these were also found to affect the retardant behavior of Eudragit.

Key words: Eudragit l-100, PEG 6000, SLS, compaction characteristics, *in vitro* release

INTRODUCTION

Controlled release dosage forms are now positioned at the forefront of many formulation strategies. This requires that attention be paid not only to the intricacies of the active pharmaceutical ingredient, but also on fine-tuning the excipients, release profile and the delivery mechanism to provide optimal therapeutic benefit. Because of their wide range of application and functionalities, especially in controlled release therapies, polymers are among the most widely used excipients (Nachaegari and Bansal, 2004).

A polymer's unique characteristics can help realize specific pharmacological benefits of an incorporated drug. The physical and chemical properties of a polymer affect its behavior in a formulation (Yuan *et al*., 2003; Agrawal *et al*., 2003; Zheng *et al*., 2005). It is expected that the chemistry of the polymer must not compromise the therapeutic action of the drug and the physical properties of the polymer must be consistent and reproducible from batch to batch. Therefore, adequate physico-chemical characterization of polymers is necessary to understand the physics of polymer-drug and polymer-polymer interactions to avoid any unwanted effects.

Additives are often incorporated in formulations to improve performance (Zheng *et al*., 2005). The effects of additives on the release of drugs from various formulations have been extensively reported (Newton *et al*., 1971; Ofoefule and Chukwu, 2000, 2001).

In the present study, a study has been made of the effects of polyethylene glycol 6000 (PEG 6000) and Sodium Lauryl Sulphate (SLS), used in drug delivery systems as release modifiers, on the compaction characteristic of Eudragit using density measurements and the Heckel and Kawakita equations for the analysis of

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the compression data (Kunle *et al*., 2003; Itiola and Alebiowo, 2005). Literature search reveals that the compaction characteristics of Eudragit alone or in the presence of additives such as PEG 6000 and SLS have not been studied.

The Heckel equation is the most widely used (Sonnergaard, 1999) for relating the relative density, D, of a powder bed during compression to the applied pressure, P. It is expressed as:

$$\text{Ln}\,[1/1 - D] = KP + A \quad (1)$$

The slope of the curve, K, is the reciprocal of the mean yield pressure, Py, of the material. The intercept of the extrapolated linear region, A, is a function of the original compact volume. It represents two stages of consolidation-one due to the initial relative density of the powder and the other due to densification by particle rearrangement. From the value of A, the relative density Da can be calculated using the following equation:

$$Da = 1\text{-}e^{-A} \quad (2)$$

The relative density of the powder bed at the point when the applied pressure equals zero, Do, is used to describe the initial rearrangement phase of densification as a result of die filling. The relative density, Db, describes the phase of rearrangement at low pressures and is the difference between Da and Do.

$$Db = Da\text{-}Do \quad (3)$$

The Kawakita equation (Itiola and Alebiowo, 2005) is used to study powder compression using the degree of volume reduction, C. The equation describes the relationship between the volume reduction of powder column and the applied pressure:

$$C = [Vo\text{-}V/Vo] = [abP/1 + bP] \quad (4)$$

Where, C, is degree of volume reduction, Vo is Initial volume, V is volume of powder column under the applied pressure P. a, b are constants characteristic to powder being compressed.

The equation above can be re arranged in linear form as:

$$P/C = P/a + 1/ab \quad (5)$$

From the graphical presentation of P/C versus P, the constants maybe evaluated. The constant a, is given as a reciprocal of the slope from the linear portion of the plot and equivalent to the value of C at infinitely high pressures. 1/ab is the intercept. a, gives an indication of the maximum volume reduction available and is considered to describe the compressibility of a powder, while b is considered to describe an inclination toward volume reduction. However, the actual physical meaning of the constants a and b have been in question (Alderborn and Nystrom, 1995). Consequently, Kawakita *et al*., 1983) have applied another equation in describing the volume reduction on tapping and vibrating processes, where the pressure P, is replaced by the tapping number, N:

$$N/C = [(1/a)\,N \div 1/ab] \quad (6)$$

Where, N is the tapping number, C is the degree of volume reduction and a and b are constants. C in equation vi is given by:

$$C = [Vo\text{-}V_N] \div Vo \quad (7)$$

Where, Vo is the initial apparent volume and VN, the volume at tapping number N. The constants of Kawakita equation can be used to estimate the flow and cohesiveness properties of powders. Constant a describes the compressibility and constant 1/b describes cohesive properties of powders or the fastness of how the final packing stage is achieved.

MATERIALS AND METHODS

Materials: The materials used were Eudragit l-100 (Lot No. 16522KG, Aldrich chemical company, Inc., USA), polyethylene glycol (PEG 6000, Cas No. 25322-68-3,) [Fluka, A.G. Switzerland], ciprofloxacin hydrochloride (Lot No. WS/GN/C2/3) and sodium lauryl sulphate (Lot No. S/5200, Evans, Nig. plc).

Methods: Preparation of granules: Granules were prepared with Eudragit as a matrix former using the wet granulation method. Eudragit alone or with the respective additives were mixed in a blender (Braun Germany). The powder mixtures consisting of 99% of Eudragit, 96.5 or 94% of Eudragit, 45.5% drug and 2.5 or 5% of the additive, respectively, were mixed for 10 min using a tumbler mixer (Karl Kolb, West Germany) and granulated with water for 5 min using an Erweka granulator (Erweka, Germany) fitted with a 1.6 mm mesh. Granules were dried at 40°C for 60 min in a hot air oven (Salvis, England). The dried granules were rescreened through a 1.7 mm sieve and lubricated with 1% magnesium stearate for 5 min using the tumbler mixer.

Five hundred and fifty milligrams tablets with and without ciprofloxacin hydrochloride (250 mg) were produced by manually compressing the granules for 60 sec with predetermined loads (at various compression pressures) using a tablet machine (THP Shanghai, Tianxiang and Chentai Pharmaceutical Machinery Co. Ltd., China) fitted with 10.5 mm flat punch and die set. Twenty tablets were compressed at each pressure. After ejection, the tablets were stored over silica gel in a dessicator for 24 h to allow for elastic recovery and hardening to prevent falsely low yield values and dimensions of the compact were determined. Dimensions were determined with a Mitutoyo model IDC1012EB (Mitutoyo Cooperation, Japan) thickness gauge to the nearest 0.01 mm. The Heckel and Kawakita plots were plotted and statistically analyzed using the Microsoft Excel computer software.

In vitro tablet properties

Hardness: Hardness of ten tablets selected at random from each batch were determined using the Monsanto hardness tester.

Friability: Ten tablets were selected randomly from each batch, dedusted weighed and subjected to abrasive shock in an Erweka friabilator at 25 rpm for 4 min. The tablets were dedusted and re-weighed. The percentage reduction in weight was calculated as the friability.

Dissolution profiles: The Erweka DT-D model dissolution assembly was used. The dissolution medium consisted of 500 mL of freshly prepared Simulated Intestinal Fluid (SIF) maintained at 37±1°C. A representative tablet from each batch and at particular compression pressure (23.5 kN) was placed in a basket, immersed in the dissolution medium and the paddle of the dissolution assembly was maintained at 75 rpm. At predetermined time intervals, 5 mL samples were withdrawn from the dissolution medium with a 5 mL pipette fitted with non absorbent cotton wool. Absorbance and concentration of withdrawn samples were read in a spectrophotometer SP160 uv/vis (Shimadzu, Japan) at wave length of 276 nm.

RESULTS AND DISCUSSION

Figure 1 and 2 show the Kawakita plots for Eudragit formulations containing PEG 6000 and SLS, respectively. An almost linear relationship between N/C and N was obtained for the formulations indicating the applicability of kawakita equation in predicting the deformation characteristic of these formulations.

The tapping experiments were performed on all samples and the constants (a and 1/b) evaluated. They

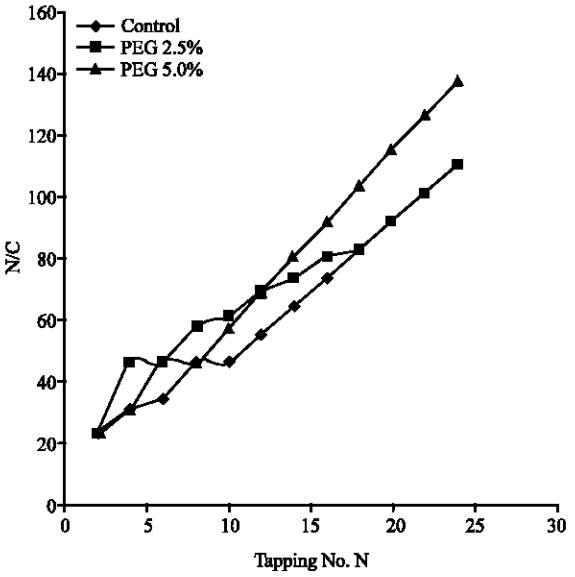

Fig. 1: Kawakita plots for eudragit formulations containing 2.5% w/w and 5.0% w/w of PEG 6000

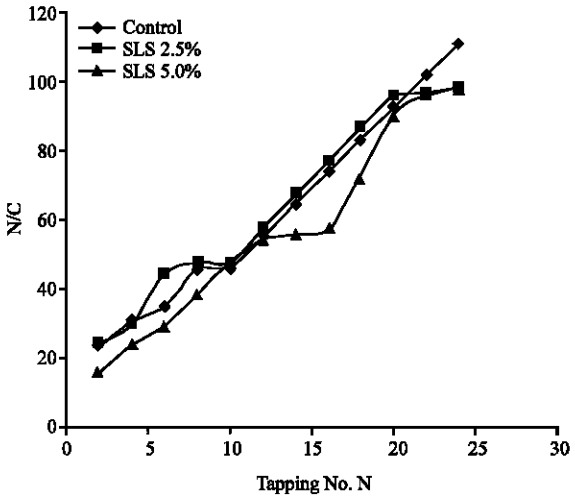

Fig. 2: Kawakita plots for eudragit formulations containing 2.5% w/w and 5.0% w/w of SLS

indicate the behavior of the powder from the bulk density to the tap density state. The constants were resolved from the slope and intercept of the graphs N/C versus C (Table 1). Small values of a (compressibility, or the amount of densification due to tapping) and 1/b (cohesiveness, or how fast or easily the final packing state was achieved) indicate good flowability and small cohesiveness (Korhonen *et al*., 2002). The results show that except for 5.0% PEG 6000, all the additives had values of "a" larger than the control. This would imply that their fluidity was poorer than that of the control. It is predicted

Table 1: Parameters obtained from Kawakita plots for eudragit tablet formulations

Matrix former/Additive	Concentration of additive (% w/w)	1/ab	1/a	A	1/b
Eudragit alone	0.0	11.59	3.99	0.251	2.91
Eudragit + PEG 6000	2.5	25.52	3.45	0.290	7.40
Eudragit + PEG 6000	5.0	8.90	5.26	0.190	1.69
Eudragit + SLS	2.5	17.54	3.60	0.278	4.88
Eudragit + SLS	5.0	7.11	3.81	0.262	1.86

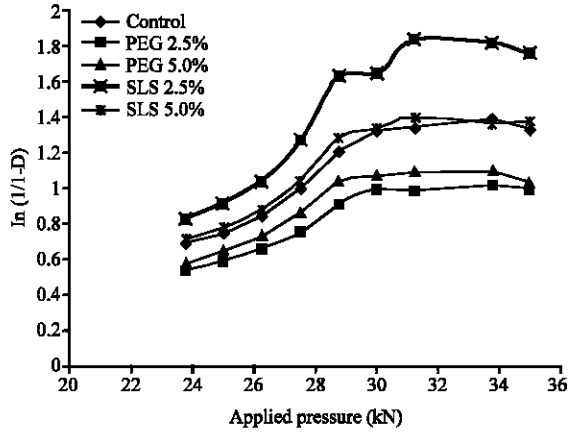

Fig. 3: Heckel plots for eudragit formulations with and without additives

that powder cohesion would increase in formulations containing 2.5%w/w PEG 6000 and 2.5% SLS, since, 1/b is also larger (Table 1) in these formulations. The lower values of 1/b for formulations containing 5.0%w/w PEG 6-000 and 5.0%w/w SLS indicate reduction in cohesion in these formulations.

Low values of 1/b indicate materials that are less cohesive and attain final packing state less readily. Table 1 shows that the values of 1/b for the formulations increased with the addition of 2.5% w/w PEG 6000 and 2.5% w/w SLS implying that at such low concentrations, the cohesiveness of the formulations was increased. However, increase in the concentration of either additive resulted in decreased values of 1/b, indicating a decrease in the cohesiveness of the formulations and its ability to attain final packing state. Generally, the formulation containing 2.5% w/w PEG 6000 had the highest 1/b value, while that with 5.0% w/w PEG 6000 exhibited the lowest value.

Figure 3 shows the Heckel plots for Eudragit formulations with and without additives. Two phases of compression are discernible in all the plots except that of 2.5% w/w SLS, which exhibited an interruption between 28 to 32 kN. PEG 6000, irrespective of the concentration used, did not alter the shape of the Heckel plot. The plots show that formulations containing SLS exhibited more compressibility than those without additives and those

Table 2: Parameters obtained from density measurements and from Heckel plots for eudragit tablet formulations

Matrix former/Additive	Concentration of additive (% w/w)	Do	Py	Da	Db
Eudragit alone	0.0	0.356	15.02	0.570	0.214
Eudragit + PEG 6000	2.5	0.291	21.69	0.405	0.114
Eudragit + PEG 6000	5.0	0.323	21.46	0.367	0.044
Eudragit + SLS	2.5	0.351	10.26	0.759	0.408
Eudragit + SLS	5.0	0.328	15.29	0.541	0.213

containing PEG 6000. It was also observed that as the concentration of SLS increased from 2.5 to 5.0% w/w, the compressibility decreased. Conversely, increase in the concentration of PEG 6000, increased the compressibility of the Eudragit granules. Other workers have reported the influence of surfactants such as SLS on Heckel plots (Krycer *et al*., 1982). Values for the mean yield pressure, Py, of the formulations were calculated from the most linear region of the plots and the intercept, A, was determined from the extrapolation of the region. The values of Da and Db were calculated from equations ii and iii respectively and are presented in Table 2.

Do values for all the formulations containing additives were lower than those without additives. The values increased with increase in the concentration of PEG 6000, but decreased with increase in the concentration of SLS. The implication of these observations is that, the initial packing of the formulations as a result of die filling decreased in the presence of additives. This was concentration dependent with PEG 6000. It could also be observed that the Do values for the formulations containing SLS were higher than those for the formulations containing PEG 6000, showing that SLS facilitated the initial packing of the granules in the die. This is in agreement with our earlier observations (Emeje and Kunle, 2004).

Db represents the rearrangement phase of the granules at low pressures. Table 2 shows that formulations containing SLS had higher Db values than those containing PEG 6000 suggesting that, more fragmentation of granules containing SLS occurred at low pressures. It can also be observed that irrespective of the type of additive used, Db values decreased with increase in their concentration.

Da values, which represent the total degree of packing, achieved at zero and low pressures are higher for the formulations containing SLS than for those containing PEG 6000. These values also decreased with increase in the concentration of the additives.

The mean yield pressure Py, is inversely related to the ability of a material to deform plastically under pressure. The values were higher for formulations containing additives (Table 2). However, they were lower for formulations containing SLS than for those containing

Table 3: Tablet properties and *in vitro* release parameters for eudragit tablet formulations containing ciprofloxacin hydrochloride

Matrix former/ Additive	Concentration of additive (% w/w)	Hardness (kg)	Friability (%)	Weight uniformity (%)	$t_{70\%}$ (min)
Eudragit alone	0.0	4.40±0.2	1.01	0.55±2.9	276.04
Eudragit + PEG 6000	2.5	8.36±0.1	0.00	0.54±4.7	-----
Eudragit + PEG 6000	5.0	7.35±0.1	0.00	0.54±3.8	68.75
Eudragit + SLS	2.5	5.80±0.4	0.00	0.55±3.5	131.25
Eudragit + SLS	5.0	5.00±0.0	0.00	0.54±3.5	-----

PEG 6000. These values suggest that, the onset of plastic deformation in the formulations containing additives occurred at higher pressures, with those containing SLS occurring at much lower pressures than those containing PEG 6000. The Py values also decreased with increase in the concentration of both additives. The Py value for formulation containing 2.5% w/w SLS was the lowest. This implies that the onset of plastic deformation in the formulation containing 2.5% w/w SLS occurred at much lower pressures than all other formulations.

Effectiveness of an adhesive agent in tablet formulation can be assessed from the hardness/crushing strength, tensile strength or from the binding capacity of tablets made from it (Ofoefule and Chukwu, 1994). The effect of additive and concentration on the hardness of ciprofloxacin tablets is shown in Table 3. Tablets without an additive exhibited lowest hardness while the hardness of batch containing 2.5% w/w PEG 6000 was the highest. Generally, tablet hardness decreased with increase in concentration of the additive from 2.5-5.0% w/w. Tablets containing SLS were softer than those containing PEG. This observed reduction of hardness, can be attributed to the high solubility of SLS which is an indication that associative forces between the molecules are weak (Kunle *et al*., 2003). Such weak associative forces appear to be exaggerated at high concentration at which the amount of the additive solubilized is expected to be high. The friability values of the tablets are presented in Table 3. The control batch that contained no additive was more friable than those with additives which produced non friable tablets. When all the evaluated tablet parameters are taken together (hardness, friability and dissolution time), no direct correlation could be established between the parameters. A correlation between hardness, friability and dissolution time should not always be expected as a result of different inherent properties of polymeric materials such as paste viscosity and compaction characteristics.

Most commonly, the results of dissolution tests are expressed in terms of the time required to release some percentage of labeled amount of the drug from the dosage form. This approach is reported to be particularly useful for quality control purposes once the dissolution characteristics of a drug and dosage form is understood (Ofoefule, 2002). The dissolution of ciprofloxacin from the tablets was evaluated using the above concept. The time taken for 70% of the drug to be released ($t_{70\%}$) was adopted to characterize the release of ciprofloxacin from the tablets. This parameter which is shown in Table 3 indicates fastest dissolution of the drug from tablets containing 5% w/w PEG followed by those containing 2.5% w/w SLS. The dissolution results show that the additives had an enhancing and retardation effect on drug release. The results show that release from tablets containing 5% w/w SLS was erratic and highly retarded. Surfactants exert a two-phase effect, which is concentration dependent. Below the critical micelle concentration (cmc), release/absorption of drugs maybe enhanced due to a better contact of the drug with dissolution medium *in vitro* or the absorbing membrane *in vivo*. Above the cmc, a portion of drug molecules may become entrapped in micelles and as such, unavailable for absorption *in vivo* or release *in vitro*. The net effect (release/absorption enhancement or retarding effect) depends to some degree on the relative magnitude of interaction between the drug and the surfactant. The release/absorption retarding effect usually predominates at higher surfactant concentrations because a larger fraction of the drug is bound to micelles. Some earlier studies (Ganderton *et al*., 1967; Levy, 1970; Braun and Parrot, 1972; Ofoefule and Chukwu, 2001) showed varying effects of SLS on drug release. In one of the studies (Braun and Parrot, 1972), SLS was found to accelerate the rate of absorption of sodium iodide by four to five times but it caused retardation in the absorption of iodoform and triiodophenol. The accelerated absorption of sodium iodide was attributed to the surface tension lowering and mucosa peptizing action of the surfactants, which resulted in better contact of the drug with the absorbing membrane. On the other hand, the retarding effect in the case of iodoform and triiodophenol was attributed to the entrapment of these drugs in the surfactant micelles. Finholt and Solvang (1968) reported that at all levels of surfactant below the cmc, the principal effect involved would be a wetting phenomenon rather than solubilization. It could, therefore, be expected that SLS may enhance or retard drug release from polymer matrices depending on its concentration, nature of the polymer, type of the drug incorporated and pH of the dissolution medium or absorbing membrane. The use of SLS as a drug release enhancer should be suggested only after

preformulation studies have proven compatibility between SLS and the drug, on one hand and SLS and the polymer, on the other hand.

CONCLUSIONS

The results presented here show that additives such as SLS and PEG 6000 affect the compaction properties of Eudragit as the matrix former. The additives were found to decrease the rate of plastic deformation of the Eudragit granules and were found to modulate the release behavior of ciprofloxacin from the matrix. SLS at concentration of 5% w/w is not suitable for this formulation.

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