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Effects of Humidity on the Dissolution Profiles of Controlled Release Theophylline Matrix Tablets Containing Release Enhancers Prepared By Melt Granulation and Coacervation Techniques

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ABSTRACT: The quantity of moisture present in tablets plays a major role in influencing the physical/chemical properties of tablets especially dissolution profiles. The purpose of the present study is to investigate the effects of relative humidity on the dissolution profiles of controlled release theophylline matrix tablets containing release enhancer prepared by melt granulation and simple coacervation techniques. Sucrose and microcrystalline cellulose at concentration of 3% w/w, 5% w/w, 7.5% w/w, and 10% w/w were included in the blends as release enhancers before compression into non-disintegrating matrix tablets. Resulting tablets were exposed to 0% and 75% relative humidity. Sample were withdrawn at 0, 15 days, 1 month, 2 months and 3 months and evaluated for cumulative drug release. Interactions were investigated using modern technology: Differential scanning calorimetry (DSC). Initial and maximum release were increased after exposure to 75% relative humidity. There was no drug – excipients interaction. Thus moisture increased theophylline release from both sets of tablets prepared by melt granulation and simple coacervation techniques.

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Granulation is a process of agglomeration of smaller powder particles to larger granules having better flow property and uniform size and shape (Dugar *et al*, 2015). Granulation is made possible with help of binders to improve bulk density, flow properties and dissolution profiles. Particles enlargement can be done by either dry or wet granulation techniques (Dugar *et al*, 2015). Several modifications of the wet technique have been adopted over the years. Two of such modifications are the melt granulation technique and the coacervation techniques. The term "coacervation" was first used by Dutch Scientists, H.G. Bungenberg de Jong and Kruyt in 1929. The term came from the Latin word "*acervus"*, meaning aggregation and the prefix *"co"* signifying the preceding union of the colloidal particles. In this process, both the drug and the polymer should be insoluble in water while a water immiscible solvent is necessary for the polymer macromolecules in solution to separate into polymer-rich droplets on addition of a non-solvent to the polymer solution (Srinidhi *et al*, 2015). This is simple coacervation technique and is brought about when temperature, pH, solvent and salt are properly chosen (Srinidhi *et al*, 2015). The procedure depends mainly on degree of hydration produced. The added substances cause two phases to be formed: one rich in colloid droplets and the other poor.

Melt granulation on the other hand involves the use of melt-able polymers e.g. waxes as the granulating agent (Avbunudiogba *et al*, 2012). Melt granulation technique has been used to prolong drug release from dosage forms (Avbunudiogba, 2019); protection of hygroscopic drugs from moisture (Avbunudiogba *et al*, 2013). It has also been used to stabilize the water soluble drug substances – dipeptidyl peptidase IV, DPP IV – (Kowalski *et al*, 2009). Certain amount of moisture is required in granules for bonds formation and thus improve compaction characteristics. Excess of moistures could also have a negative effect on solid dosage forms. Hydrolysis which is the breaking of molecular bond brought about by presence of water (moistures) is a major cause of chemical degradation (Lieberman and Vemuri, 2015). Hydrolysis is important in the degradation of proteins and polypeptides (Lieberman and Vemuri, 2015). Hydrolytic degradation may lead to an unacceptable appearance. Degradation of excipients in solid dosage forms may be a critical factor in its instability. This include degradation of antimicrobial preservatives, fading of dyes used to colour products or degradation of antioxidants (Darji *et al,* 2018). In the present study, the effects of moisture on the physical properties (such as dissolution profiles) of controlled release theophylline matrix tablets containing release enhancers will be investigated.

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MATERIALS AND METHODS

Materials: (a) Theophylline: The test drug (theophylline powder) was obtained from Vital Biotic, Nigeria Ltd.

(b) *Excipients:* Samples of Eudragit®RL100 and Eudragits®RS100 were received as free samples from Evonik Industries AG – Werk Röhm, Darmstadt. Carnauba wax, sucrose, microcrystalline cellulose (MCC) and absolute ethanol (BDH, Poole, England). Normal saline (Unique Pharmaceutical Nigeria Ltd), magnesium stearate and talc (Analytical grade). All other chemicals used were of analytical grade and were used without further purification.

Methods: To formulate theophylline matrix tablets, two sets of granules were prepared by melt granulation (Avbunudiogba *et al*, 2012) and simple coacervation techniques (Avbunudiogba, 2019).

Melt granulation: Wax coated granules of theophylline were prepared according to the method described by Avbunudiogba *et al* (2012). A sample of carnauba wax (4.5 g) was weighed and melted in a stainless steel container in a hot water bath at 90 ± 0.5ºC. A sample of theophylline (30 g) was added to the molten wax and stirred continuously. While still hot the mass was forced through a sieve (710 µm) and allowed to cool in an air conditioned room at 20 ± 0.5ºC for 4 h.

Coacervation: In order to form granules by coacervation techniques, an ethanolic (30 ml) solution of theophylline (30 g) and acrylate-methacrylate copolymer (Eudragits®RL100, i.e. 15%) was formed; followed by addition of 270 ml of normal saline to co-precipitate the drug and the polymer. The mixture was allowed to stand for 30 min and the precipitate (coacervates) collected by filtration. The coacervates were dried in hot air oven at 60 ± 0.5ºC for 24 h and the dried mass was carefully passed through a sieve (710 µm aperture) to obtain granules.

Tablets compression: In order to form the matrix tablets, the granules formed by melt granulation and coarcervation techniques (equivalent to 300 mg theophylline) were also mixed with 1% w/w talc, 1% w/w magnesium stearate and varied concentrations (3% w/w, 5% w/w 7.5% w/w and 10% w/w) of either sucrose or microcrystalline cellulose (release enhancers) before compression to non-disintegrating (matrix) tablets using multiple punch tableting machine (Manesty machine Ltd, B3B, Liverpool, England) at 28 arbitrary units on the load scale.

Differential scanning calorimetry (DSC): Interactions were investigated using "Differential Scanning Calorimetry (DSC)". The spectra of pure theophylline powder and that of formulated theophylline tablets were obtained using Differential Scanning Calorimeter (DSC 204F1, Phoenix NETZSCH, Germany) equipped with thermal analysis system. The instrument was calibrated using indium (156.88ºC) as internal standard and dry Nitrogen was used as the purge gas (purge 20 ml/min). Seven milligram (7 mg) of the desiccated samples of theophylline were weighed into an aluminium pan and covered with a perforated lid. The probes were heated at a temperature of 25 – 500ºC at a rate of 5ºC/min. The glass transition (Tg), cold crystallization (Tcr) and melting (Tm) temperatures were then evaluated using a Computer Proteus software.

Tablets dissolution test: Dissolution test was carried out according the method described by Avbunudiogba (2019) using the rotating basket method (USP apparatus one). A tablet was place in the basket which was rotated at a speed of 100 rev. per min in the dissolution medium. Samples (5ml) of the leaching fluid were withdrawn at specified time interval with a pipette plugged with cotton wool.

The samples were filtered through a number 3 Whatman(R) filter paper, diluted properly with fresh dissolution medium and analyzed with UV spectrophotometer (PG Instrument, USA) at a wavelength of 272 nm. Fresh dissolution medium (5 ml) was added each time a sample was withdrawn in other to maintained sink condition. The experiment was done in triplicate and mean value reported.

Effects of relative humidity on dissolution profiles of tablets: Effects of relative humidity of dissolution profiles of tablets was carried out on selected representative samples of the formulations. Tablets were exposed to 0% and 75% relative humidity (0% RH and 75% RH) at room temperature (30 ± 2ºC). Samples were withdrawn after 30 days and evaluated for cumulative drug release.

In order to obtain 0% RH, a desiccator was charged with activated silica gel (desiccant). While a concentrated sodium chloride solution was placed in air tight glass chamber to obtain 75% RH.

RESULTS AND DISCUSSION

Table 1 showed the dissolution parameters of the selected batches (i.e. BF2 and BF5) obtained from the dissolution profiles shown in Figures 1 and 2. It was observed that both prompt/initial release (*Mi)* and maximum release (M_∞) increased when the tablets were exposed to 75% RH.

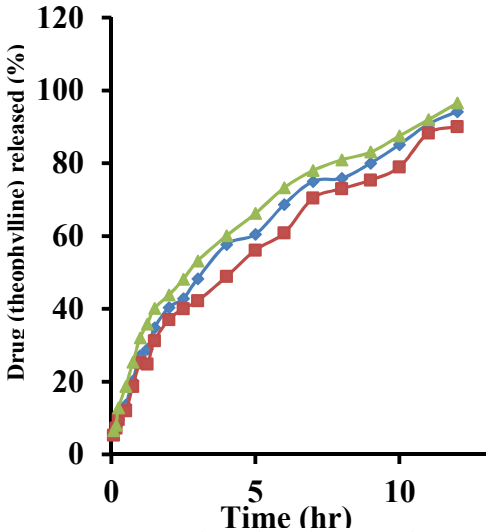

Figure 1a: Percentage drug release from carnauba wax granulated theophylline tablets (BF2h) containing MCC: Before storage (—♦—), after storage at 0% RH (—■—) and 75% RH (—▲—) at room temperature (i.e. 30ºC) for 30 days

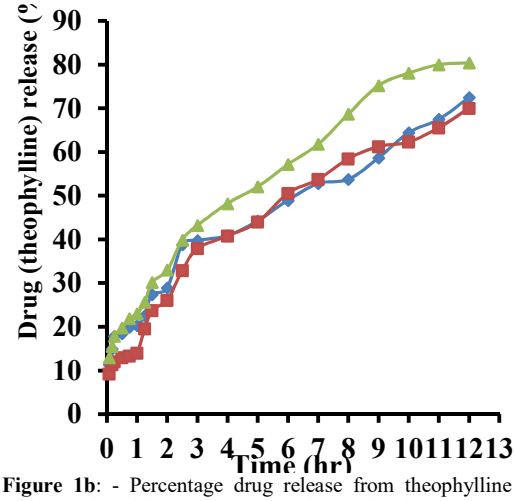

Figure 1b: - Percentage drug release from theophylline matrix tabletsproduced by coacervatuon using Eudragit®RS100 (BF5h) & containing MCC: Before storage (—♦—), after storage at 0% RH (—■—) and after storage at 75% RH (—▲—) all at room temperature (i.e. 30ºC) for 30 days.

For instance, batch BF2h which was produced by melt granulation and contained 7.5% w/w MCC; initial release (Mi) increased from 27.2% to 32%; while maximum release (M_∞) increased slightly from 94.2% to 96.5%. The time to attained maximum release remained constant, thus the rate of release increased from 7.9%h^{-1} to 8.9%h^{-1} when tablets were exposed to 75% RH. This finding (i.e. increase rate of release) is not unconnected with swelling of the tablets and weakening of interparticulate bonds due to moisture sorption (Hiew *et al*, 2016). Weakening of particles bonds in tablets could results to collapse of the matrix system leading to dose dumping in the gastrointestinal track and increase plasma concentration which could be hazardous (Wu and McGinity, 2000).

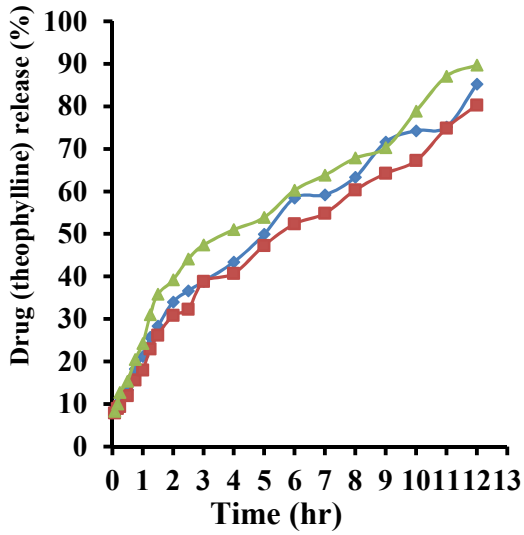

Figure 2a: - Percentage drug release from carnauba wax granulated theophylline tablets (BF2*l*) & containing sucrose: Before storage (—♦—), after storage at 0% RH (—■—) and after storage at 75% RH (—▲—) all at room temperature (i.e. 30ºC) for 30 days.

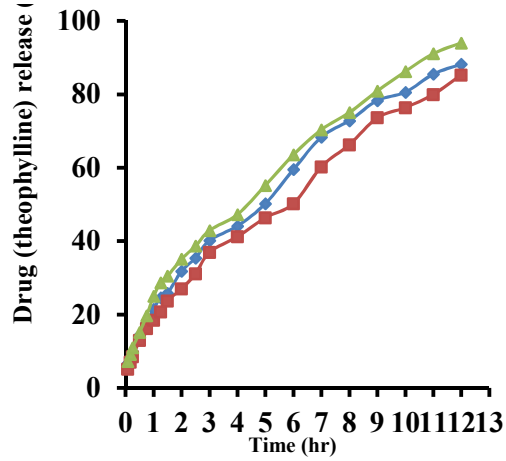

Figure 2b: Percentage drug release from theophylline matrix tablets produced by coacervatuon using Eudragit®RS100 (BF5*l*) & containing sucrose: Before storage (—♦—), after storage at 0% RH (—■—) and after storage at 75% RH (—▲—) at room temperature (i.e. 30ºC) Eudragit®RS100

Accordingly, the various dissolution parameters (i.e. Mi, M_∞, and M_∞/t_∞) were found to decrease when the various tablets were exposed to dryer atmosphere (i.e. 0% RH). This is expected as it will take some time for tablets to absorb moisture, swell and bonds broken for dissolution to occur. Similar finding were recorded when matrix tablets containing leaching agent (sucrose) – i.e. batches BF2*l* and BF5*l* – were subjected to the different relative humidities. Here channels were created following moisture sorption prior to dissolution study, hence greater prompt release (*Mi*) and maximum release (M_∞).

The DSC thermograms of pure theophylline powder and the formulated dosage forms are shown in **Figure 3**. The first peak - which is a trough in the thermogram

of theophylline – was observed at a temperature of 272.1ºC (**Figure 3A**). Pure theophylline is known to melt between 270ºC and 275ºC (BPC, 2009). The melting of theophylline is an endothermic process, hence the observed trough in **Figure 3A**. Above this temperature (i.e. melting point), another trough was observed at a temperature of 322.5ºC. This second trough is a clear indication of theophylline degradation.

Table 1: Effect of relative humidity (RH) on the dissolution parameter (M_∞, Mi, M_∞/t_∞) of matrix tablets after storage for 30 days at room temperature (30 ± 2ºC).

Batch	Dissolution parameter	Before exposure to Relative Humidity (RH)	After exposure to RH	
			0% RH	75% RH
Melt granulation technique				
BF2	M_∞ (%)	54.6	51.4	58.0
	M_i (%)	17.0	15.5	19.4
	t_∞ (h)	12.0	12.0	12.0
	M_∞/ t_∞ (%h^{-1})	4.6	4.3	4.8
BF2h	M_∞ (%)	94.2	90.0	96.5
	M_i (%)	27.2	25.1	32.0
	t_∞ (h)	12.0	12.0	12.0
	M_∞/ t_∞ (%h^{-1})	7.9	7.5	8.9
BF2*l*	M_∞ (%)	85.2	80.3	89.7
	M_i (%)	21.3	18.0	24.2
	t_∞ (h)	12.0	12.0	12.0
	M_∞/ t_∞ (%h^{-1})	7.1	6.7	7.5
Coacervation technique				
BF5	M_∞ (%)	46.4	43.6	49.6
	M_i (%)	14.7	12.3	16.0
	t_∞ (h)	12.0	12.0	12.0
	M_∞/ t_∞ (%h^{-1})	3.9	3.6	4.1
BF5h	M_∞ (%)	72.5	70.0	80.4
	M_i (%)	20.3	14.0	23.0
	t_∞ (h)	12.0	12.0	12.0
	M_∞/ t_∞ (%h^{-1})	6.0	5.8	6.7
BF5*l*	M_∞ (%)	88.2	85.3	94.0
	M_i (%)	21.5	18.5	25.0
	t_∞ (h)	12.0	12.0	12.0
	M_∞/ t_∞ (%h^{-1})	7.4	7.1	7.8

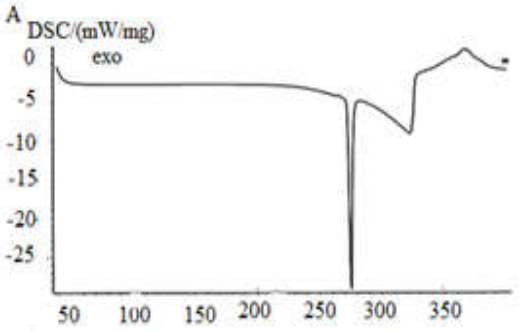

Figure 3A: DSC thermogram of: pure theophylline powder

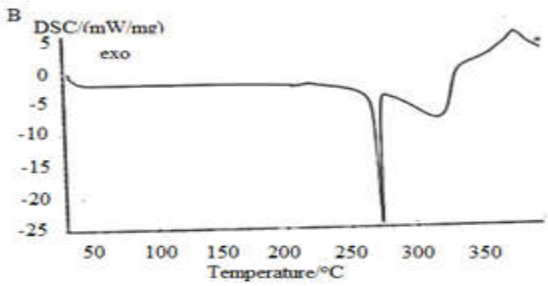

Figure 3B: DSC thermogram of: Theophylline matrix tablets produced by coacervation technique using Eudragit®RS100 (BF5)

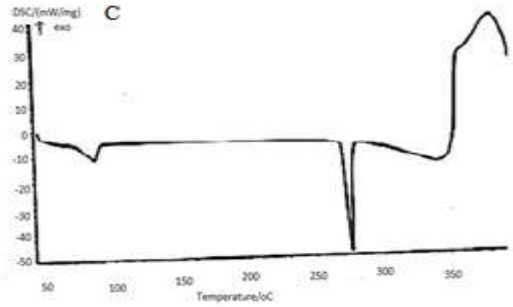

Figure 3C: DSC thermogram of: Theophylline matrix tablets produced by melt granulation using carnauba wax (BF2)

Similar peaks (2 troughs) were observed in all the formulations roughly at the same position with that of pure theophylline powder (**Figure 3B and 3C**). These observations indicated the fact there is no drug – excipients interaction; however, the slight differences were probably due to the presence of these excipients and not chemical reactions leading to formation of new/different compounds (Al-Obaidi and Buckton, 2009).

Conclusion: This study has further revealed the profound effect of moisture on the dissolution profiles of matrix tablets. Moisture of 75% relative humidity (75% RH) has more damaging effect, while that of 0% relative humidity (0% RH) has little or no effect. Thus storage of theophylline matrix tablets in a dry place will assure stability of the product. Also, it will be preferred to store theophylline matrix tablets in blister packs or bottles of 100 tablets or less for daily administration than in bottles of 1000 tablets where frequent exposure would lead to moisture sorption and subsequent degradation.

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