Published in final edited form as:

Int J Pharm. 2019 January 30; 555: 380–393. doi:10.1016/j.ijpharm.2018.11.045.

Exploratory studies in heat-assisted continuous twin-screw dry granulation: A novel alternative technique to conventional dry granulation

Venkata Raman Kallakunta¹, Hemlata Patil¹, Roshan Tiwari¹, Xingyou Ye¹, Sampada Upadhye², Ronald S Vladyka², Sandeep Sarabu¹, Dong Wuk Kim⁴, Suresh Bandari¹, and Michael A. Repka^{1,3}

¹Department of Pharmaceutics and Drug Delivery, School of Pharmacy, The University of Mississippi, University, MS 38677

²Catalent Pharma Solutions, 14 School House Road, Somerset, NJ 08873, USA

³Pii Center for Pharmaceutical Technology, University of Mississippi, University, MS 38677, USA

⁴College of Pharmacy, Kyungpook National University, Daegu 41566, South Korea

Abstract

Dry granulation is the preferred technique for solvent-sensitive products, especially drugs with stability problems such as hydrolysis. Twin-screw granulation is a continuous granulation technique, offering a potential alternative to conventional dry granulation techniques such as roller compaction. The major advantage of twin-screw granulation is the ability to adjust process parameters of dry granulation without compromising the compression properties. This study was aimed to perform exploratory studies of heat-assisted continuous twin-screw dry granulation process to formulate sustained release tablets for APIs with different melting points: theophylline, acetaminophen and lidocaine hydrochloride hydrate. Granulation feasibility was studied with different binders (e.g. KlucelTM EF, Kollidon® VA64), sustained release agents (e.g. KlucelTM MF, Eudragit® RSPO) and diluents at various drug loads. The processing conditions were below the melting point or glass transition temperature of the formulation ingredients. After successful granulation, DSC and XRD studies revealed the crystalline nature of the granules and FTIR studies showed no interaction of the API with the excipients. The granules were compressed into sustained release tablets without any compressibility issues. The tablets were stable after testing for 6 months at 25°C/60% RH. This novel continuous dry granulation technique may offer an excellent alternative to conventional dry granulation techniques.

*Corresponding author: Michael A. Repka, D.D.S., Ph.D., Professor and Chair, Department of Pharmaceutics and Drug Delivery Director, PiiCenter for Pharmaceutical Technology School of Pharmacy University of Mississippi, University, MS 38677, USA Phone: 662-915-1155 Fax: 662-915-1177, marepka@olemiss.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declaration of Interest statement: None

Keywords

Dry granulation; granule strength; binder; twin-screw granulation; glass transition temperature

1. Introduction

Granulation is an important step in the manufacture of solid dosage forms, as it ensures flowability, compactibility and processability of raw materials for conversion into the final dosage form (Monteyne et al., 2016b). Generally, the most common methods employed for granulation are wet granulation, fluidized bed granulation, dry granulation and melt granulation. For some APIs and excipients, solvent granulation can present serious challenges, such as stability or degradation of the product (Lakshman et al., 2011). Hot-melt granulation is another technique that exploits a molten binder to form agglomerates in the granulation process, avoiding the drying step. In melt granulation, the probability of physicochemical interactions between the molten binder and the other formulation ingredients is high and this may pose a threat to product stability (Hamdani et al., 2003).

The dry granulation technique provides the advantages such as cost effectiveness as no solvent is required, elimination of the drying step and improved stability compared with other granulation techniques. It is particularly useful in formulations with components sensitive to hydrolysis and heat (Vervaet and Remon, 2005). When direct compression is not suitable, dry granulation is the preferred choice and the manufacturing classification system (MCS) should assist the selection of the best suitable process for a particular formulation (Leane et al., 2015). Dry granulation mechanisms include the formation of strong bonds, such as solid bridges between the particles, weaker intermolecular bonds such as van der Waals forces, hydrogen bonds, electrostatic bonds and mechanical interlocking (hooking) of irregularly shaped particles. (Adolfsson et al., 1997). Solid bridges can be formed between particles with plasticity and simple molecular structures; however, in pharmaceutical products, van der Waals forces and hydrogen bonding are mostly observed between the particles (Adolfsson et al., 1997; Nystrom et al., 1993). Generally, roller compaction is conventionally performed in dry granulation (Mangal et al., 2016). The main drawback of conventional dry granulation is the loss of strength after the re-compression step, which arises from the resistance to permanent plastic deformation due to the complexity of rearrangements involved at a particular level, explained by Malkowska et al. (1983) as the process of “work hardening”. Sun and Himmelspach (2016) explained how the reduction of surface area has an adverse effect on tablet strength and Nordstrom and Alderborn (2015) reported that porosity was a positive factor in the production of tablets with acceptable mechanical strength.

At present, twin-screw granulation is used as an alternative to other granulation techniques as it is a continuous process that offers many advantages, such as a high production rate, reduced variability, improved product quality, cost savings and time savings (Plumb, 2004; Vervaet and Remon, 2005). The technique of twin-screw granulation has been extensively reported as an alternative to conventional batch techniques such as wet granulation and hot-melt granulation (Keleb et al., 2004; Walker et al., 2006). However, more focus is required in

the area of twin-screw dry granulation, as it has the potential to solve the problems faced by conventional dry granulation processes (Liu et al., 2018; Upadhye et al., 2017). The dry granulation process in current study may be a potential alternative to conventional granulation techniques. As stated previously, wet granulation involves solvents that may lead to serious stability problems for the formulations. Melt granulation can also promote stability issues due to interaction between the formulation ingredients in the molten state. Conventional dry granulation methods, such as roller compaction, experience quality problems such as a lack of sufficient strength in the granules when they are recompressed. Therefore, the twin-screw dry granulation technique, which is assisted by temperatures below the melting point or the glass transition temperature of ingredients, may present a useful option in terms of product quality and stability. As this granulation technique does not involve solvent or molecular level melt mixing, it may overcome issues such as hydrolysis due to solvents and degradation due to exposure to high temperatures. In addition, the shear associated with granulation helps the proper distribution of binders between the particles of the blend, improving granule properties as well as quality of the tablets. The current study has focused on the development of sustained release (SR) tablets by using twin-screw dry granulation that employed processing conditions below the glass transition temperature (T_g) or melting point of the ingredients in the formulation. The main objective of this work was to assess the feasibility of dry granulation for the production of granules with good compression characteristics for all three of the APIs investigated. To develop successful SR tablets for the APIs, different SR polymers and binders were selected based on the physicochemical properties of the respective APIs. The relationship between the physicochemical properties of formulation ingredients on the percentage of drug loaded into the granules and their effects on the drug release profiles was also investigated.

2. Materials and methods:

2.1. Materials

Theophylline (THP) anhydrous was purchased from Sigma Aldrich (USA); acetaminophen (APAP) was purchased from Mallinckrodt (MO, USA); lidocaine HCl.H₂O (LDH) was purchased from AK Scientific Inc. (CA, USA); Klucel™ EF and Klucel™ MF (hydroxy propyl cellulose) and Aqualon™ T10 (Ethyl cellulose (EC)) were supplied by Ashland (DE, USA); Eudragit® RSPO (USA) was a gift sample from Evonik; and Kollidon® VA64F was a gift sample from BASF (USA). The diluents Avicel® PH 102, Avicel® DG (microcrystalline cellulose; MCC) were gift samples provided by FMC Biopolymer (USA) and magnesium stearate was purchased from Ferro (USA). All chemicals employed in the study were of analytical grade.

2.2. Selection of excipients and preparation of physical blend

Excipients play an important role in the feasibility of process and stability of a pharmaceutical dosage form. Low-viscosity grade binders (MW: 45000–80000) Klucel™ EF (viscosity: 300–600 mPa.s; particle size: 595 µm) and Kollidon® VA64F (viscosity: 25–31 mPa.s; particle size: 20 µm) were selected as they are known not to interfere with the SR properties of the formulations. Owing to excellent compressible properties and extensive use in dry granulation techniques, micro crystalline cellulose (MCC) was selected as a diluent

for the granulation process (Ingelbrecht and Remon, 1998). The formulation compositions were designed to assess the feasibility of successful granulation with different APIs at different drug loads with various SR agents. The compositions of the SR tablet formations are shown in Table 1. The quantity of each ingredient (except lubricant) was accurately weighed and sifted through a #30 ASTM mesh. The ingredients were blended in a V-Shell blender (Maxiblend®, Globe Pharma) for 15 min at 20 RPM.

2.3. Twin-screw granulation

Twin-screw granulation was performed on an 11mm twin-screw extruder (Process11, Thermo Fisher Scientific) equipped with a gravimetric feeder. The feed rate for each formulation was calibrated before the granulation process. The temperature settings for the formulations with different APIs are shown in Table 2 and Zone 1 (the feeding zone) was maintained at ambient temperature. The temperature of the granules during the granulation was checked at two points. The temperature was determined by using an infrared temperature gun at Zone 5 (maximum temperature zone) and at the discharge point by the collection of samples at 3 min intervals. The temperature of granules was within $\pm 2^{\circ}\text{C}$ – 4°C of the maximum temperature zone (Zone 5), in which the temperature was set below the lowest M.P. or Tg of any component in the formulation. A screw configuration (screw configuration I) with one mixing zone (with seven mixing elements at an angle of 60° to each other) at Zone 5 was employed in the early trials (Fig. 1). However, the trials resulted in poor granulation, producing more than 40% of fines ($<100\mu$). Based on the results of granulation, an alternative screw configuration (screw configuration II), with two mixing zones with first mixing zone (with seven mixing elements at an angle of 60° to each other) at Zone 5 and a second mixing zone at Zone 7 (with five mixing elements at an angle of 30° to each other) was tested. Finally, screw configuration III with first mixing zone in Zone 5 (with seven mixing elements at an angle of 60° to each other) and a second mixing zone (with five mixing elements at an angle of 30° to each other) at zone 8 (just before the discharge element) was selected. The die plate of the extruder was removed to aid the collection of the granules from the extruder. The residence time of the blend in extruder was determined by the addition of food color blue powder into the feeding zone after the barrel was filled with physical mixture. The time between the addition of the color and the time of the first appearance of color in the granules discharging from the extruder was reported as the residence time. During the process, granules were collected 15–20 min after the start of process to allow the torque to stabilize and ensure the quality of the granules was uniform throughout the process and approximately 150 g of granules were collected for each batch. The physical appearance of the granules and torque generated during the entire granulation process were recorded for all the formulations. The granules obtained were placed at room temperature and allowed to cool. After cooling, the granules were milled at 600 RPM by using a Fitz Mill L1A (Fitzpatrick®) and sifted through a #25 mesh ASTM. The granules were lubricated with magnesium stearate (sifted through #60 mesh ASTM) on a Maxiblenner® at 20 RPM for 3 min.

2.4. Evaluation of size distribution and granule strength

Particle size distribution was determined for the milled granules by sieve analysis using a vibratory sieve shaker (Performer III SS-3, Gilson Inc.). The analysis was conducted by

using a pre-weighed sieve nest combination of #30, 40, 60, 80, 120, and 200 ASTM mesh series. An accurately weighed quantity (10 g) of sample was discharged into the sieve nest and the analysis was conducted for 10 min at an amplitude of 5 with a tapping rate of 60 taps/min. The retained amount of powder on each sieve was accurately weighed after the analysis. Based on the weight distribution and the particle size distribution plots were generated.

The granule strength and stiffness were determined before the milling process. Granule strength was determined as the primary breaking force at which the macroscopic granule characteristics depreciated and, finally, granule breakage occurred. The stiffness of the granules was expressed as the derivative of the contact force with respect to displacement (Russell et al., 2014). The granules were cut to a size of approximately 0.8–1 mm by using sharp scissors and the fraction of granules sized 0.9–1.00 mm was collected and subjected to evaluation of strength by TA-XT2i texture analyzer with exponent software (Texture Technologies Corporation, New York). A stainless-steel cylindrical probe (diameter, 7 mm) was used to test the individual granules. The adhesive tape to which the granules were fixed for the test was affixed to a stainless-steel platform. The analysis was performed at a probe speed of 0.1 mm/s. The analysis was conducted on a single granule and a minimum of 25 granules from each batch were evaluated for strength and stiffness. The granule strength and stiffness values were expressed as the average of all the tested granules for each formulation.

2.5. Flow properties

The flow properties of physical mixture and twin-screw granules were assessed through the evaluation of the angle of repose and Carr's index (Carr Jr, 1965).

$$\text{a) Angle of repose: } \tan(\theta) = \frac{h}{r} \quad (2)$$

h = height of the pile

r = radius of pile at base

$$\text{Carr's index (CI): } CI = \left(\frac{D_T - D_B}{D_T} \right) \times 100 \quad (3)$$

D_T = Tapped density

D_B = Bulk density

2.6. Preparation of SR Tablets

The SR tablets were prepared from the compression of lubricated granules into tablets (600±10 mg) by using an 11 mm diameter (round) flat punch. The tablets were compressed with a such a force as to maintain the tablet hardness of 14–16 KP on the Piccola 10 station

tablet compression machine set up with a gravimetric hopper at a turret speed of 20 RPM. The compressed tablets were evaluated for assay and content uniformity.

2.7. Physical characterization of the tablets

The compressed SR tablets were evaluated for physical properties such as weight variation, hardness and friability as per compendial procedures. The mechanical strength of the tablets was determined by using a hardness tester (Schleuniger, Pharmatron) and friability was measured by using an FT2 friability tester (Schleuniger, Pharmatron).

2.8. Fourier transform-infrared spectroscopy (FTIR)

Fourier transform-infrared spectroscopy (FTIR) studies were conducted on an Agilent Cary 660 FTIR Spectrometer (Agilent Technologies, Santa Clara, CA) in the spectral range of 4000–600 cm^{-1} . The analysis was to monitor the interaction between the excipients and the API in a physical mixture and twin-screw granules. The bench equipment was armed with an ATR (Pike Technologies MIRacle ATR, Madison, WI), which was fitted with a single-bounce, diamond-coated ZnSe internal reflection element.

2.9. Differential scanning calorimetry (DSC)

DSC analysis was performed by a TA DSC 25 instrument using Trios software (TA Instruments, Waters LLC, DL, USA). Approximately 5 mg of sample was weighed and hermetically sealed in an aluminum pan and an empty aluminum pan was used as reference in this experiment. The heating rate of the experiment was 10°C/min and temperature range was set dependent upon the melting point of API in the respective formulation. The analysis was performed under an N₂ (inert) atmosphere with a flow rate of 20 mL/min.

2.10. X-ray diffraction (XRD) analysis

The XRD analysis of the APIs, physical mixtures, and dry granules was performed on Rigaku X-ray equipment (D/MAX-2500PC, Rigaku Corporation, Tokyo, Japan) equipped with a copper tube anode using a step width of 0.02°/s over a range from 5° to 40° on a 2 θ scale at room temperature. The experimental current, voltage, and scanning speed were maintained at 100 mA, 40 kV and 10°/min respectively.

2.11. In vitro drug release studies

The in-vitro release studies for SR tablets were conducted by using an USP apparatus type II (SR8-plus™, Hanson) maintained at 37°C $\pm$ 0.5°C and 50 RPM (n=6). The dissolution study was performed in 300 mL of 0.1N HCl (pH 1.2) for the first 2h, followed by phosphate buffer (pH 6.8) with a total media volume of 1000 mL for the remainder of the period (up to 24h). Aliquots of 3 mL were collected at predetermined time intervals (1,2,4,6,8,10,12,16,20, and 24h) and an equivalent volume of fresh medium was replenished at each time point. The samples were filtered through a 0.45 μm membrane filter and the UV absorbance at 272 and 247 nm was used to estimate the theophylline and APAP content respectively.

Lidocaine HCl.H₂O content was quantified by HPLC with an isocratic elution (Waters Corp., Milford, MA, USA) equipped with an auto sampler, UV/VIS detector and Empower

software. The analytical column Phenomenex Luna C18 (5µm, 250 mm × 4.6 mm) was used to analyze the quantity of API at a detection wavelength of 254 nm and the flow rate of 1 mL/min. A modified USP 40 analytical method was followed in this study. The mobile phase comprised a 1:4 mixture of acetonitrile: buffer (930:50 of water and glacial acetic acid) adjusted to pH 3.40 by the addition of 0.1N NaOH. The samples were passed through a 0.45µm filter (Millex® GV, Durapore® PVDF) before an aliquot of 10 µL was injected into the column.

2.12. Drug release kinetics

The in-vitro drug release data of formulations were evaluated by various mathematical models (zero-order, first-order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas) to assess the mechanism of drug release (Costa and Lobo, 2001; Higuchi, 1963; Korsmeyer et al., 1983).

The first order model was:

$$Q = Q_0 e^{kt} \quad (7)$$

Where Q denotes the amount of drug released in time t, Q_0 represents the initial drug amount, and k is the rate constant.

The zero order model was:

$$Q = Q_0 - kt \quad (8)$$

Where Q is the drug released in time t, Q_0 denotes the initial drug amount, and k represents for the rate constant.

The Higuchi model was:

$$Q = kt^{1/2} \quad (9)$$

Where Q is the amount of drug released in time t, and k represents the rate constant.

The Korsmeyer-Peppas model was:

$$Q = kt^n \quad (10)$$

Where Q is the amount of drug released in time t, k represents the rate constant, and n is the diffusion exponent, which designates the mechanism of drug release.

The Hixson-Crowell model was:

$$Q_0^{1/3} = Q_t^{1/3} + kt \quad (11)$$

Where Q_t is the drug released in time t , Q_0 represents the initial drug amount, and k denotes the rate constant.

2.13. Stability studies

The stability studies were conducted at 25°C/60% RH for 6 months. Thirty tablets from each formulation were placed in an HDPE container and the containers were placed in a stability chamber (Caron, 6030). The samples were analyzed for assay content uniformity and drug release after 1,2,3 and 6 months. The results were evaluated and the similarity factor (f_2) was determined as per the implementations of the US FDA and the drug release profiles between the fresh and stability samples were compared.

The f_2 value defines the logarithmic transformation of the sum of the squared error of differences between the fresh and stability samples was calculated from the following equation:

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{i=1}^n (R_i - T_i)^2 \right]^{-1/2} \times 100 \right\} \quad (12)$$

Where R_i is the cumulative drug release rate of the fresh product, T_i denotes cumulative release rates of the stored product at the predetermined time point and n is the number of time points. An f_2 value of 50 indicates similarity between the drug release profiles of the fresh and stored samples.

2.14. Statistical analysis

The statistical analysis of the in-vitro drug release profiles was performed by using GraphPad Prism (Version 5.0, GraphPad Software Inc., La Jolla, CA, USA). One-way ANOVA followed by Tukey's multiple comparison test was performed to compare the drug release profiles of different formulations. For values of $p < 0.05$ the differences were considered statistically significant.

3. Results & Discussion

3.1. Effect of formulation ingredients in twin-screw granulation

The twin-screw granulation was performed on different APIs based on their melting points and the thermal properties of excipients in the formulation (Table 1). The processing conditions were selected to ensure that each ingredient in the formulation remained in a nonmolten (dry) form. The maximum temperature employed in the process was below the T_g /M.P of the ingredient of the blend with the lowest T_g or MP (Table 2). The effect of different formulation variables on the feasibility of formation of granules was studied. The nature of the API and the excipients affected the feasibility of successful granulation. The

type of SR agent and binder were selected based on the MP of the API and accordingly the processing conditions. The selected SR agents differed in their physicochemical properties and compaction properties. MCC was selected as a diluent as it is reported to have more plasticity than other diluents such as lactose and mannitol which are relatively brittle (Kaialy et al., 2016). MCC was also reported to be thermally insensitive owing to its higher melting point than diluents such as mannitol and lactose (Krok et al., 2017). Preliminary granulation trials were conducted with API loads of 20%–50% for all formulations. For each API, the maximum possible drug load was identified in preliminary studies and further trials were performed with the maximum possible drug load. The visual observations and other granule formation properties are presented in Table 3.

In theophylline formulations, the SR agents studied were EC (viscosity: 8–11 mPa.s), Klucel™ MF (viscosity: 4000–6500 mPa.s) and their combination was also investigated. It was observed that a maximum of 50% drug-loaded granules could be produced, with good compressibility into tablets and less than 5% of fines in the granules. As an inefficient granulation process would produce more fines and lead to compromised flow and the tablets produced would show poorer tableting properties such as “work hardening” (Gamble et al., 2010). Among all the SR agents, Klucel™ MF was able to produce granules in formulations F1 and F2 without the addition of binder, as Klucel™ MF itself possess good binding properties. EC provided the least assistance in granule formation for all APIs and did not produce satisfactory results of granulation when formulated along with the binders Klucel™ EF (particle size: 595 µm) or Kollidon® VA 64 (particle size: 20 µm) up to 10% concentration of each binder. The combination of Klucel™ MF and EC (F3) in equal proportions with an additional 5% binder resulted in successful granulation. This indicated the impact of the formulation ingredients that assist in the successful granulation process. This kind of granulation behavior might be due to the binding efficiency of Klucel™ MF, which resulted in closely bound particles that formed aggregates (granules). Moreover, the greater binding properties of Klucel™ MF allows it to create more solid bridges and consolidate the bonds between the ingredients of the formulation, resulting in successful granulation. (Mohammed et al., 2012). EC, which is not a binder and is less plastic in nature, made the granulation process relatively not feasible in the range of processing temperatures (Tewari and Durig, 2014). The binder proportions in the F4 and F5 formulations were designed to compensate for the non-plastic nature of EC. As the percentage of fines in F5 was lower (<5%) than that in F4 (15%–20%), F5 was considered for the tablet compression step instead of F4.

A similar trend was observed in the APAP formulations, but the maximum API load that could be incorporated into granules and compressed into tablets was 40%, owing to the lower compactibility of APAP compared with THP. As F10 produced a greater percentage of fines (approximately 20%), in formulation F11, the binder content was adjusted to limit the percentage of fines to <5%; hence, F11 was considered for the tablet compression step instead of F10. The LDH formulations exhibited the lower granulation properties with a maximum drug load of 30%. However, this might have resulted from the poor compactibility of API. Although the binders play a major role in binding the components of the formulation into granules, it was observed that diluents also assist in the binding process. Therefore, the total binding properties of the formulation comprise a synergistic effect of binder and diluent

(Mangal et al., 2016). Owing to the poor compactibility of LDH, a lower drug load was possible. To compensate this increased proportion of excipients with good binding properties was incorporated into the LDH formulations to improve granule formation. More than 25% of fines in granules were produced when LDH was combined with the diluent Avicel® 102; this was also due to the poor compactibility of LDH. The diluent Avicel® 102 (particle size of 100 µm) therefore was replaced with Avicel® DG (particle size of 50 µm), a finer grade of MCC, and resulted in less than 5% of fines in granules. As reported by Gundlach and Blum (2012) the finer particle size of Avicel® DG will promote more surface area for contact between particles leading to more adhesive van der Waals forces between the ingredients of physical mixture. Eventually, this leads to a more compact and denser physical mixture of the formulation with an overall reduction in the percentage of fines in the granules (Stepani and Milošević, 2009). The temperature conditions were same for formulations with Avicel® 102 and Avicel® DG, but the overall surface area of formulations with Avicel® DG might be higher and led to the formation of denser granules. These results were in accordance with the observations reported by Krok et al. (2017). The proportion of Eudragit® RSPO was found to inversely affect the formation of granules. The granulation was not possible when Eudragit® RSPO was used (F17 and F18) with a single binder or a combination of the binders Klucel™ EF or Kollidon® VA64F, for a binder proportion of up to 15%. This was due to the resistance of Eudragit® RSPO to plastic deformation and insufficient binder quantity, and resulted in an accumulation of the material under the mixing zones (Fig. 2); consequently, the torque was raised above the maximum allowable limit of the extruder after 10–15 min of operation and the process was immediately shut down.

The melting points of APIs were in the order THP > APAP > LDH owing to the differences in their physical properties. THP was found to be more feasible in terms of higher drug loaded granule formation, which was a result of the more compact nature of API in granulation. The other two APIs were fluffy powders with lower compressibility and their proportion inversely affected the percentage of drug loading. The drug-loading efficiency occurred in the order LDH < APAP < THP, which was in accordance with the order of the crystallinity of the API (THP > APAP > LDH) demonstrated by the XRD results (Section 3.8). The peak intensities of the APIs in the XRD studies were in the order of THP > APAP > LDH. This difference in the crystallinity of the API affected the percentage drug loading during granulation, because the compactibility of the crystalline portion of the formulation was assisting the remaining excipients, which have good binding or plastic deformation properties, in granulation. The heat transfer occurring in particle to particle interactions results in the formation of adhesive van der Waals bonds and consequently, favors the granulation process. Another reason was their bulk densities, which were found to be 0.439 g/mL for THP, 0.336 g/mL for APAP and 0.339 g/mL for LDH. The highest crystallinity associated with the relatively greater bulk density of THP can be attributed to the highest drug loading in granulation. In contrast, the low compressibility of LDH observed during granulation resulted from its lowest crystallinity and relatively low bulk density (Gundlach and Blum, 2012; Yun and Santamarina, 2008). Overall, it was observed that the crystallinity of the API and the compressibility of the excipients were the deciding factors in granulation and compressibility into tablets without any capping and lamination issues. Similar observations were reported by Mangal et al. (2016). Capping problems usually occur

because of poor cohesivity between the particles due to the non-granular portion and the greater proportion of fine or fractured particles or a lack of binder in the formulation (Wu et al., 2007). The presence of EC and Eudragit® RSPO had a negative effect on granule formation owing to their lower plasticity. The ability of Klucel™ MF as a dry binder to form granules resulted from its good binding property, higher viscosity than the other binders (viscosity: 4000–6500 mPa.s), non-reversible plastic deformation and propensity to form solid bridges (Liu et al., 2018). In this study, as the process temperature was below the T_g of the polymers, the shear produced in the twin-screw granulation method in conjunction with thermal energy, supported granulation. The trials F6, F12, F17, and F18 did not result in successful granulation because of the high proportion of non-plastic excipients (EC and Eudragit® RSPO) in the respective formulations. In these formulations, even high binder content was not helpful for the production of granules owing to the poor compactibility of the remaining excipients.

3.2. Effect of screw configuration on granulation

Initial granulation trials with screw configuration I with one mixing zone configuration (with seven elements at an angle of 60° to each other) (Fig. 1) at Zone 5 resulted in partial granulation with more than 35%–40% of fines (below 100µm) and caused problems during tablet compression. Therefore, to reduce the proportion of fines, the alternative screw configuration II, with two mixing zones, was chosen. Screw configuration II, containing first mixing zone configuration at Zone 5 (with seven elements at an angle of 60° to each other) and a second mixing zone at Zone 7 (with five elements at an angle of 30° to each other), resulted in successful granulation. The granule formation was strengthened by the additional mixing zone and the granules formed contained a relatively lower content of fines (15%–20%). However, it was observed that the granules were crushed underneath the elements before they were discharged. Therefore, to further reduce the percentage of fines, screw configuration III was designed. This screw configuration included two mixing zones, with the first mixing zone (with seven elements at an angle of 60° to each other) at Zone 5 and a second mixing zone (with five elements at an angle of 30° to each other) at Zone 8, just before the discharge elements. The screw configuration III resulted in a lower percentage of fines (<5%). In the twin-screw dry granulation process, the binder and other of the formulation pass through the extruder as separate immiscible phases because of their non-molten state. The granule formation was supported by kneading at the mixing zones and the distribution of binder throughout the blend (Monteyne et al., 2016a). The shear produced owing to the angle between the mixing elements helps the proper distribution of each of the components and the distribution of the binder, which led to the formation of stronger bonds between the components. The generation of shear was associated with the formation of granules with lower % of fines in successful granulation trials. The proper location of an additional mixing zone further endeavored to strengthen the granules, resulting in the production of quality tablets without any tableting problems such as capping and lamination.

3.3. Effect of feed rate on torque for formulation with different APIs

Granule formation was observed to be successful between 30–100 RPM (Table 3). It was observed that a higher extruder screw speed (>75 RPM) resulted in a relatively higher percentage of fines. All the formulations ran at lower speeds (<40 RPM) caused relatively

higher torque, whereas formulations ran at higher speed (>75 RPM) resulted in lower torque. The granules were observed to be elongated structures rather than compact granules at higher speeds (>75 RPM), which could be associated with lower torque values. This may be a result of insufficient shear inside the barrel and a shorter process time, which led to poor granulation as the dry material was pushed through the barrel at a faster rate. The increase in the feed rate improved the barrel fill at a specific screw speed, thereby increasing the compactness between the particles aided by the distribution binder and subsequently favoring granule formation. Similar observations were reported by Dhenge et al. (2018). The increased interaction between the particles which are yet to be granulated and already formed granules in motion, caused the interlocking of these particles on the granule surface, improved granule size and strengthened the granules formed (Kumar et al., 2014). However, above a certain feed rate (7 g/min), oversized long lumps ($> 5000 \mu\text{m}$) were produced, causing capping and lamination problems during tablet compression. This behavior was due to an imbalance between the shear produced in the barrel and the quantity of feed filled between the screws. This type of particle size is the opposite phenomenon to conventional processes such as wet granulation and similar results were reported by Liu et al. (2018). Based on these results the final RPM and feed rate fixed for the process were 40 and 4–5 g/min. The torque values were observed to be related to the compactibility of the APIs in successful granulation trials. The THP formulations resulted in relatively higher but manageable torque values than other APIs. THP conferred better compaction properties than other APIs, which was reflected in the torque values and resulted in a high drug-loading percentage. The granulation properties of LDH were poor compared with THP and APAP and the torque values agreed with the physical observations: the fluffy nature of the API might be another reason for the relatively low percentage of drug loading. In all the successful granulation trials the torque values were within the maximum limits of operation (table 3), indicating the feasibility of the granulation process. The non-plastic nature and poor compressibility offered by EC affected the process feasibility in formulations containing THP and APAP. Similarly, LDH formulations with Eudragit® RSPO were less suitable for the dry granulation process and torque variations in the remaining formulations were dependent only on the total proportion of Klucel™ polymers, because the strong interlocking (binding) observed between the particles in the formulation promoted granulation (Djuric and Kleinebudde, 2008).

3.4. Particle size distribution and mechanical properties of granules

The particle size distribution (PSD) data in Fig. 4 indicates the possibility of granule formation based on the fraction of granule size. The excipients with greater binding properties produced a greater fraction of granules above $250 \mu\text{m}$ in size. In theophylline formulations, the fraction of granules above $250 \mu\text{m}$ size was affected by the presence of Klucel™ MF and the size of the granules was proportional to the concentration of Klucel™ MF (F1 and F2). In the formulation F3 with a combination of Klucel™ MF and EC, the granule size was lower owing to the relative non-plasticity of EC. The fraction of granules above $250 \mu\text{m}$ was approximately 47% in formulations with a combination of EC, whereas it was approximately 75% in the formulation with Klucel™ MF alone. In APAP formulations, a similar trend was observed with the Klucel™ MF proportions. Moreover, when half of the Klucel™ MF was replaced with EC, (F9) there was a drop in the percentage of granules

above 250 μ m. This was due to the resistance of EC to granulation, which was balanced by the plasticity of the other components which helped in successful granulation. In addition, a smaller proportion of Kollidon® VA64F in the blend promoted finer granules owing to its small particle size (20 μ m). Mangal et al. (2016) reported similar observations. A similar trend was observed in LDH formulations also. These results indicated the role of the excipients in granulation at conditions below their Tg as well as the MP of the drug in respective formulations. The binding properties of the excipients play an important role in the process of granule formation as well as being a determining factor in the particle size of formed granules. The good binding properties of the ingredients in the formulation, the greater the ease of granule formation and the larger the granule size.

The mechanical properties of the granules are presented in Table 4. The granule strengths of formulations of different APIs resulted in only small differences, which may be a result of the adjustment of drug load and binder content to achieve successful granulation in the granulation studies. The type of binder used in the formulation, as well as the formulation composition, affected the stiffness values of the granules. Among all the formulations, the formulation that contained Klucel™ MF as a binder resulted in formation of stiffer granules than the other formulations consisting of binders and other polymers with a lower molecular weight. Although the stiffness values did not result in a proportional increment with the proportion of polymer in the composition, they were representative of the effect of the binding agent on the physical properties of the granules. The difference can be attributed to a greater difference of molecular weight and number of alkyl substitutions between the polymers in the formulations (Desai et al., 2006). In the case of amorphous polymers, the process of plastic deformation is regulated by the molecular motion in segments of the polymeric chains. After the critical stress point, the factors that control the physical nature of the granules at breakage are the molecular weight of the polymers and polymer chain entanglements. Thus, as Klucel™ MF has a higher molecular weight and more hydroxyl propoxyl substitutions than other binders, this might be the reason for greater stiffness of the formulations containing Klucel™ MF (Meijer and Govaert, 2005). The changes in the composition with different molecular weight polymers influence the physical properties of granules (Klompen et al., 2005). The solid bridges of the binder spread throughout the granule led to different textural properties of the binders.

3.5. Evaluation of flow properties of the granules and tableting

The granules of all formulations were evaluated for their flow properties after milling and the granules of all formulations showed good to excellent flow properties, as presented in Table 5. The formulations exhibited successful granulation showed good compression properties and there were no issues of capping and lamination in tableting. This indicates that sufficient granule strength and good plastic deformation of granules was achieved and that tablets with acceptable mechanical properties were produced. Usually, problems such as capping may be observed in dry granulation owing to insufficient bonding between the particles despite a good contact area between them (Bozic and Vrecer, 2008). In this study, in case of successful granulation these problems were not observed and the tablets obtained showed the desired mechanical strength. The shear produced with this method is because of the mixing elements and the angle between them. This is entirely different from the

conventional methods like roller compaction. The angle between the mixing elements provides the shear due to which the components of the blend are well distributed with each other while passing through the mixing zones. This kind of distribution with the aid of binder produced granules which resulted in tablets with good mechanical strength without any capping and lamination issues. This may be due to the suitability of selected excipients in the process and the optimization of drug load in the respective formulations.

3.6. FTIR analysis

The FTIR spectra of the APIs, the physical mixture and the formulations are presented in Fig. 5. The infrared spectra of theophylline showed a characteristic peak at 1660 cm^{-1} , which represents the imide group of the heterocyclic ring; the N-H stretching vibration was observed at 3120 cm^{-1} , the C-N stretching vibration was observed at 1238 cm^{-1} , and the N-H bending vibration was observed at 1562 cm^{-1} (Gunasekaran et al., 2005).

For APAP, the peaks at 1609 cm^{-1} and 1435 cm^{-1} represent aromatic ring C-C stretching; the peak at 3323 cm^{-1} represents the N-H amide stretching vibration; the peak at 1561 cm^{-1} was recognized as the N-H in plane bending; the peak at 1662 cm^{-1} represents the C=O stretching vibration; peaks between $1258\text{--}1225\text{ cm}^{-1}$ represent C-N and/or C-O stretching vibrations; and the peak at 1328 cm^{-1} represents the O-H bending vibration (Ebrahimi et al., 2016). In LDH, the characteristic peaks at 3455 cm^{-1} and 3383 cm^{-1} represented N-H stretching and the peak at 1656 cm^{-1} represented C=O stretching (Wei et al., 2015). All formulations showed the characteristic peaks of the APIs in their respective formulations; this indicated that there was no interaction between the API and other excipients under the studied processing conditions.

3.7. DSC studies

The DSC thermograms of APIs and all formulations are presented in Fig. 6. The peaks were observed at 273.6°C , 170.7°C , and 82.9°C in the pure APIs of THP, APAP, and LDH, respectively. The formulations F1, F3, F5, F7, F9, F11, F13, F15 and F16 showed the melting peak of respective API, which indicated that the crystalline form of the API was present in the granules. The main reasons for the presence of the crystalline form of the API are that the processing temperature is below the melting point of the API in the formulation and the shear assisting the thermal process is optimum, which did not affect the native crystalline nature of the API studied. The observed temperatures at different zones in the barrel were practically within the range of $\pm 2\text{--}4^{\circ}\text{C}$ of the set conditions during the process, which indicated the feasibility of the process and the shear associated with temperature was observed to have no effect on the crystallinity of the API.

3.8. XRD analysis

The XRD spectra of the APIs, respective physical mixtures, and the formulations are presented in Fig. 7. Theophylline showed characteristic crystalline peaks at 2θ values of 12.6° , 7.1° , 14.3° , 24.0° , 25.5° and 26.1° . APAP showed characteristic peaks with the greatest intensities at 2θ values of 18.1° , 24.3° , 15.5° and 20.3° . LDH showed peaks at 2θ values of 24.9° , 16.5° , 25.8° and 14.0° . The peak intensities of the APIs (Fig. 7d) were found to be in the order of $\text{THP} > \text{APAP} > \text{LDH}$, which indicated the order of crystallinity of the

APIs according to their melting points. The crystalline nature of APIs was reflected in granulation studies, as the crystalline nature of the drug was assisting in the granulation and the percentage drug loading followed the same order as the crystallinity. All formulations showed the peaks of the appropriate APIs at 2θ . The polymers KlucelTM MF, KlucelTM EF and Kollidon® VA64F were reported to be amorphous and without any specific crystalline pattern (Arndt and Kleinebudde, 2017). The characteristic peaks at 22.8° , 20.6° , 14.8° and 12.1° represent MCC. EC, reported to be a mostly amorphous polymer, showed some less intense and broad peaks at 19.7° , 8.4° and 21.2° (Mahnaj et al., 2013). In formulations of THP, APAP, and LDH, the same characteristic crystalline peaks were observed at 2θ for the respective APIs, MCC and EC.

In the twin-screw process, it may be expected that the shear produced by the screw elements in the barrel could raise the temperature to such an extent that it may melt the physical mixture. In our study, the temperature setting was below the M.P. or Tg of the components of the formulation and the process was observed to be within the range of set temperature conditions. The FTIR, DSC, and XRD spectra indicated that the granules formed retained the crystalline nature of their respective formulations, no interactions between the components of the formulation occurred and the processing conditions employed were well suited to the dry granulation process.

3.9. In vitro drug release

As shown in Fig. 8, the dissolution profiles of the formulations prepared with different APIs showed different release patterns based on their composition. The tablets were physically observed during the dissolution study and the physical state of the matrix was recorded. The variation in the physical stability of the tablet matrix during release studies was found to be related to the % drug released. The factors that played a vital role in the release behavior were the nature of the excipients and the physical behavior of the tablet matrix during the dissolution study.

In theophylline formulations, the tablets with KlucelTM MF showed good matrix integrity and sustained drug release for up to 24h. The formulations consisting of only KlucelTM MF (F1 and F2) showed very minimal erosion (approximately 5%) over 24h. The drug release was incomplete in these formulations, which may have been owing to the high molecular weight (850,000) and viscosity (476.2 and 471.9 mPa.s for a 1% solution at pH 1.2 and 6.8) of KlucelTM MF. This high viscosity of KlucelTM MF might be the reason for the low variation in the drug release profiles of F1 and F2, despite their different proportion of KlucelTM MF. The excellent binding properties and viscosity of KlucelTM MF resulted in a dosage form with good matrix integrity, which then became one of the controlling factor for drug release. As these higher molecular weight polymers were reported to enhance gelling properties in aqueous medium, the viscous gel layer formed owing to the high molecular weight of KlucelTM MF retarded the drug diffusion (Durig et al., 2002). In formulation F3 with EC and KlucelTM MF, the matrix showed erosion behavior from 6h onwards and almost 75% of the matrix was eroded at the end of study. This erosion behavior may reflect the non-plastic nature of EC, which caused the erosion of the tablet when exposed to aqueous medium. The F2 formulation resulted in low drug release owing to KlucelTM MF. The inclusion of EC and

Klucel™ MF in F3 was expected to further retard the drug release from formulation F3, as EC is a water insoluble and a non-swellable polymer. However, the proportion of EC did not have any significant effect on the dissolution compared with formulation F2, which contained only Klucel™ MF at a lower proportion. Thus, the high viscosity of Klucel™ MF might be the governing factor in drug release. The F5 formulation, which included only EC, showed relatively lower matrix integrity; the drug release was complete in 20h, whereas the formulations F1, F2, and F3 showed drug release percentages of 44.4%, 54.16%, and 51.06% respectively by the end of study. The lower matrix stability of the tablet matrix and the quicker drug release in F5 may be a result of the low molecular weight binders, such as Klucel™ EF and Kollidon® VA64F, (80,000 and 45000–70000 respectively and viscosity (245.4 and 258.3 mPa.s for a 1% solution at pH 1.2 and 6.8, respectively) which were reported to undergo greater erosion owing to their fast gelation properties. This may have destabilized the tablet matrix and promoted faster drug release (Arndt and Kleinebudde, 2017). The drug release profile of the F5 formulation was observed to be significantly different ($p < 0.05$) to formulations F1, F2, and F3. The gel thickness acts as a barrier and increases the drug diffusion path length. The thicker the gel, the greater the hindrance to drug diffusion; conversely, the lower the molecular weight, the weaker the gel, resulting in greater drug release (Rajabi-Siahboomi et al., 1996). In summary, the presence and proportion of Klucel™ MF in the formulation was observed to be the key factor governing drug release from the matrix. Although ethyl cellulose is water-insoluble, in contrast with the hydrophilic nature of Klucel™ MF, the compactness provided by Klucel™ MF and its high viscosity were vital in the control of drug release.

In the formulations of APAP the tablet integrity was observed to be lower than the THP formulations containing similar SR agents and binders. The tablets of all formulations showed erosion of the particles from 2h and the matrix was completely disintegrated within 8 h, except for formulation F7 (which was stable for up to 12 h). A significant difference ($p < 0.05$) was observed between the drug release of F7 and the rest of the formulations (F8, F9, and F11) in the first 2 h. The initial high drug release in first 2h was correlated with the change in matrix integrity due to erosion, which was subsequently reflected in drug release pattern. Here, in the case of APAP, although these results were correlated with the properties of Klucel™ MF and EC, the drug release was controlled by the compactness provided by the API fraction to the matrix. APAP has a higher aqueous solubility (14.7 g/L) (Yalkowsky et al., 2010) than theophylline (7.36 g/L) (Kalantzi et al., 2006), APAP has relatively lower compactibility than theophylline, as evidenced by granulation studies. Thus, the greater solubility and lower compactibility of APAP might be the reasons for the destabilization of tablet matrix and faster dissolution rate. Another reason for the lower stability of the matrix in the medium may be the faster hydration of the outer matrix gel. The change in matrix integrity in the medium over the time, polymer dissolution and polymer-polymer interactions (with neighboring molecules in the polymer chain) could have weakened the integrity of the gel layer. With the progression with time the central matrix was also affected by the progressive erosion pattern promoted from outer gel layer and led to the complete loss of integrity owing to the abrupt alteration in the rheological properties of gel layer (Narasimhan and Peppas, 1997).

Unlike the THP and APAP formulations, LDH formulations were mostly non-disintegrating in nature. This might be due to the low permeability nature of Eudragit® RSPO in combination with the highly viscous Klucel™ MF. The matrices showed good integrity until the end of study and much less erosion of particles, whereas the formulations with a lower proportion of Klucel™ MF (F14 and F15) showed approximately 10%–15% erosion of particles at the end of study. This might be a result of relatively lower viscosity of the formulation than that of F13 and the hydrophilic portion of Klucel™ MF. The results indicated that the variation in Klucel™ MF proportion affected the drug release. The non-disintegrating nature of the matrix might be a reason for the lower variation in the release profiles of LDH formulations. The F16 formulation showed the longest SR profile owing to the combination of Klucel™ MF and water-insoluble Eudragit® RSPO. Based on physical observations of all formulations, a slow drug release was expected as the matrix was intact until the end of study. However, approximately 30%–40% of the drug release was observed in the first 2h, which indicated that the release of the drug from surface layers occurred initially before the gel layer was formed in the tablet. This may be attributable to the release of the drug from the outer layers of the tablet. The higher initial drug release may be attributable to the poor compactibility of LDH observed during granulation studies. When compressed into tablets, these granules may be unable to hold the LDH unlike THP and APAP tablets. Although the granules were compressed into tablets without any compression issues, the tablets could not control drug release in first 2 h after exposure to medium. After 2h, the remainder of the drug release was sustained for up to 24h and this might be because of the stronger gel formation towards the inner core of matrix by Klucel™ MF with the increased residence time of the tablet in the medium. The presence of Eudragit® RSPO, a polymer with low aqueous solubility, further hindered the drug release in the F16 formulation. Owing to relatively the poor compaction found in LDH, the formulations with a combination of Klucel™ MF and Eudragit® RSPO were produced with the aid of binders Kollidon® VA64F and Klucel™ EF. Formulation F16, which contained 10% Kollidon® VA64F, resulted in lower drug release than F15. This may have been due to the relatively lower water-soluble proportion resulting from the absence of Klucel™ EF portion and the very good binding properties of Kollidon® VA64F, owing to the fine particle size (20 µm), which led to its efficient distribution in the matrix. (Herting and Kleinebudde, 2007).

In summary, the THP based formulations had greater drug loading than the APAP based formulations and better matrix integrity during dissolution studies. This was a reflection of the nature of the granules formed, the type of matrix produced after compression and the aqueous solubility of the API. As a higher amount of drug was released into the media in the first few hours and the spaces created in the matrix further weakened the tablet matrix, this was followed by complete disintegration of the APAP tablets. In LDH formulations, although the drug loading was low and a large proportion of the drug was released in the first few hours, as matrix integrity was maintained by the excipients, the remaining drug release was sustained for up to 24h.

3.10. Release kinetics

The release kinetics data of the formulations with different APIs are presented in Table 6. The drug release from the matrix could be a result of many mechanisms, including diffusion,

erosion, or even a combination of mechanisms. The release kinetics varied in the formulations employed and all formulations with different APIs. The release kinetics data revealed that the R^2 values for zero-order kinetics were greater than those for the first-order release kinetics (Table 6). All the formulations were a good fit to the Korsmeyer-Peppas equation. As the polymeric systems contain swellable polymers, water-insoluble polymers, combination of both types, most of the formulations may follow a combination of mechanisms responsible for drug release (Glaessl et al., 2010). Theophylline formulations with KlucelTM MF (F1, F2, and F3) followed Fickian diffusion with n value below 0.5, whereas the F5 formulation with EC in combination KlucelTM EF showed a non-Fickian diffusion, which indicated the possibility of both drug diffusion and the relaxation of the polymer chain (Lamoudi et al., 2016). This implied that the high molecular weight polymer KlucelTM MF played a role in controlling the drug release through the control of the matrix erosion and drug diffusion through firm gel. F3, with the combination of EC and KlucelTM MF, showed similar release kinetics to F1 and F2, which contained only KlucelTM MF as the SR agent. This showed that the viscosity of KlucelTM MF was the controlling factor in the drug release pattern. In formulation F5, the lower viscosity binders KlucelTM EF and Kollidon® VA64 could not form a strong gel around the tablet. As time progressed in the dissolution study, the tablets showed relatively greater erosion and the release occurred by a non-Fickian diffusion mechanism.

In APAP-based formulations, the matrix showed relatively lower physical stability compared to THP formulations. The kinetics observed were different to THP formulations as the matrix integrity appeared to be affected by the amount of APAP released from the matrix as the study progressed. The effect of SR polymers was interfered by the continuous erosion of the matrix and was reflected in the release pattern. These different results might be a result of a combination of effects, such as relatively quick erosion of the matrix owing to high aqueous solubility and lower compaction provided by the API. This might have resulted in the complete hydration of the outer matrix gel layer, which leads to disentanglement of the polymer matrix, proceeding to the central core until complete erosion of matrix occurred (Nokhodchi et al., 2012). The continuous erosion of tablet matrix might be intrusive with the basic behavior of hydrophilic and hydrophobic polymer chains and eventually the release kinetics was different. In this study, the APAP formulation results were different to those expected, which indicated the role of the API in the release pattern when the other formulation ingredients were the same.

As the formulation ingredients were different in LDH-based formulations, the physical behavior of tablet was completely different from that of the THP and APAP formulations. The tablets were physically stable and less erosion occurred. This might be due to the combination of KlucelTM MF with the water-insoluble methacrylate derivative Eudragit® RSPO. The polymer Eudragit® RSPO is reported for diffusion-based release mechanisms (Zhu et al., 2002). In these formulations, approximately 30%–40% of the drug was released within the first 2h, which might be due to the dissolution of the API in the outer matrix associated with the hydrophilic polymer owing to rapid hydration that occurred during the initial hours of study. Although the drug loading was relatively low in LDH formulations, the poor compactibility offered by LDH during granulation might be explain the initial quick release of the drug. Although the granules were compressed into tablets without any

compression issues, the tablet matrix might not be able to hold the drug in the first hours of its encounter with the release medium. As the time progressed, the SR polymers appeared to affect control of the drug release. In the combination formulations, this caused anomalous drug diffusion and further release was controlled by the inner portion which was a combination of Klucel™ MF and insoluble Eudragit® RSPO. In the formulations with higher proportion of Klucel™ MF (F13) only, Fickian diffusion was observed where the gel layer strength was greater owing to higher concentrations of highly viscous Klucel™ MF and the possibility of virtual cross-linking of polymer chains with a higher concentration of hydrophilic polymers (Chaibva et al., 2010).

Collectively, it was observed that the release kinetics varied not only with the nature of excipients, but also with the nature of the API and the integrity provided by it to the tablet in the dissolution media over the time period.

3.11. Stability studies

After the stability studies, the formulations showed no differences to the fresh samples with respect to the physical properties, drug release and assay. The assay values of THP (98.31 ± 1.71 – 102.40 ± 0.94), APAP (97.94 ± 1.21 – 102.28 ± 2.29) and LDH (97.16 ± 1.07 – 103.51 ± 1.86) were within the acceptable limits established by USP 40. The f_2 (>50) values of the in-vitro drug release profiles were in the range of 77.3–61.2 for THP, 62.5–54.2 for APAP and 71.2–66.4 for LDH compared to initial samples suggested similarity in drug release profiles. The release kinetics were found to be unchanged after 6 months of storage at 25°C/60% RH. The unaltered behavior of all formulations was an indication of the stability of the dosage forms and suggested that the processing conditions were well-suited to formulate SR tablets through dry granulation. The processing conditions that engaged all the ingredients in a non-molten state improved the probability of good stability for all formulations.

4. Conclusion

The heat-assisted twin-screw dry granulation process was successfully accomplished for the formulations with APIs of different melting points and the processing conditions were below the MP/Tg of all the components of the respective formulations. This study investigated the preliminary aspects of heat-assisted twin-screw dry granulation. The ability of all APIs to form granules under dry processing conditions was evaluated and the effects of drug loading and the screw configuration were also observed. The influence of binders on successful granulation was studied for different APIs, different SR agents and the effect of the binder proportion on the production of the desired granules with a specific API was investigated. The tablets produced from the dry granules exhibited good mechanical strength as shown by the results. The applicability of heat-assisted twin-screw granulation as an alternative technique to conventional dry granulation techniques was investigated for different formulations with varying thermal and compaction properties. This novel study covers the basic aspects of heat-assisted dry granulation and could bring good insights into the applicability of continuous twin-screw granulation, which may ameliorate the process constraints and stability problems in conventional granulation techniques. This exploratory

study of heat-assisted twin screw granulation provides guidance for future dry granulation studies of different APIs, formulations and process constraints via twin- screw technology.

Acknowledgements:

This work was supported by Catalent® Pharma Solutions. This project was also partially supported by Grant Number P20GM104932 from the National Institute of General Medical Sciences and the Biopharmaceutics-Clinical and Translational Core E of the COBRE, a component of the National Institutes of Health.

Abbreviations:

APAP	Acetaminophen
API	Active pharmaceutical ingredient
ASTM	American society for testing and material
CI	Carr's index
DSC	Differential scanning calorimetry
EC	Ethyl cellulose
FTIR	Fourier transform-infrared spectroscopy
HPC	Hydroxy propyl cellulose
HPLC	High performance liquid chromatography
LDH	Lidocaine hydrochloride hydrate
M.P	Melting point
MCC	Microcrystalline cellulose
SR	Sustained release
Tg	Glass transition temperature
THP	Theophylline
XRD	X-Ray diffraction

References:

- Adolfsson Å, Olsson H, Nyström C, 1997 Effect of particle size and compaction load on interparticulate bonding structure for some pharmaceutical materials studied by compaction and strength characterisation in butanol. *European journal of pharmaceutics and biopharmaceutics* 44, 243–251.
- Arndt O-R, Kleinebudde P, 2017 Influence of binder properties on dry granules and tablets. *Powder Technology* 10.1016/j.powtec.2017.04.054.
- Bozic DZ, Vrečer F, 2008 Influence of dry granulation on compactibility and capping tendency of macrolide antibiotic formulation. *International journal of pharmaceutics* 357, 44–54. [PubMed: 18308490]
- Carr RL, Jr, 1965 Evaluating flow properties of solids. *Chem. Eng.(Jan.)* 18, 163–168.

- Chaibva FA, Khamanga SM, Walker RB, 2010 Swelling, erosion and drug release characteristics of salbutamol sulfate from hydroxypropyl methylcellulose-based matrix tablets. *Drug development and industrial pharmacy* 36, 1497–1510. [PubMed: 20528615]
- Costa P, Lobo JMS, 2001 Modeling and comparison of dissolution profiles. *European journal of pharmaceutical sciences* 13, 123–133. [PubMed: 11297896]
- Desai D, Rinaldi F, Kothari S, Paruchuri S, Li D, Lai M, Fung S, Both D, 2006 Effect of hydroxypropyl cellulose (HPC) on dissolution rate of hydrochlorothiazide tablets. *International journal of pharmaceutics* 308, 40–45. [PubMed: 16321490]
- Dhenge RM, Fyles RS, Cartwright JJ, Doughty DG, Hounslow MJ, Salman AD, 2010 Twin screw wet granulation: granule properties. *Chemical Engineering Journal* 164, 322–329.
- Djuric D, Kleinebudde P, 2008 Impact of screw elements on continuous granulation with a twin- screw extruder. *Journal of pharmaceutical sciences* 97, 4934–4942. [PubMed: 18300301]
- Durig T, Skinner G, Harcum W, 2002 Compression and Drug Release Characteristics of Directly Compressible KLUCEL® Hydroxypropylcellulose Controlled Release Matrix Systems. *Pharmaceutical Technology Report PTR-019-1*, Ashland.
- Ebrahimi A, Saffari M, Dehghani F, Langrish T, 2016 Incorporation of acetaminophen as an active pharmaceutical ingredient into porous lactose. *International journal of pharmaceutics* 499, 217–227. [PubMed: 26768724]
- Gamble JF, Tobyn M, Dennis AB, Shah T, 2010 Roller compaction: application of an in- gap ribbon porosity calculation for the optimization of downstream granule flow and compactability characteristics. *Pharmaceutical development and technology* 15, 223–229. [PubMed: 22716462]
- Glaessl B, Siepmann F, Tucker I, Rades T, Siepmann J, 2010 Mathematical modeling of drug release from Eudragit RS-based delivery systems. *Journal of Drug Delivery Science and Technology* 20, 127–133.
- Gunasekaran S, Sankari G, Ponnusamy S, 2005 Vibrational spectral investigation on xanthine and its derivatives—theophylline, caffeine and theobromine. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 61, 117–127.
- Gundlach B, Blum J, 2012 Outgassing of icy bodies in the Solar System–II: Heat transport in dry, porous surface dust layers. *Icarus* 219, 618–629.
- Hamdani J, Moës AJ, Amighi K, 2003 Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets. *International journal of pharmaceutics* 260, 47–57. [PubMed: 12818809]
- Herting MG, Kleinebudde P, 2007 Roll compaction/dry granulation: Effect of raw material particle size on granule and tablet properties. *International journal of pharmaceutics* 338, 110–118. [PubMed: 17324537]
- Higuchi T, 1963 Mechanism of sustained- action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of pharmaceutical sciences* 52, 1145–1149. [PubMed: 14088963]
- Inghelbrecht S, Remon JP, 1998 Roller compaction and tableting of microcrystalline cellulose/drug mixtures. *International Journal of Pharmaceutics* 161, 215–224.
- Kaialy W, Khan U, Mawlud S, 2016 Influence of mannitol concentration on the physicochemical, mechanical and pharmaceutical properties of lyophilised mannitol. *International journal of pharmaceutics* 510, 73–85. [PubMed: 27242312]
- Kalantzi L, Reppas C, Dressman J, Amidon G, Junginger H, Midha K, Shah V, Stavchansky S, Barends DM, 2006 Biowaiver monographs for immediate release solid oral dosage forms: Acetaminophen (paracetamol). *Journal of Pharmaceutical Sciences* 95, 4–14. [PubMed: 16307451]
- Keleb E, Vermeire A, Vervaet C, Remon JP, 2004 Twin screw granulation as a simple and efficient tool for continuous wet granulation. *International journal of pharmaceutics* 273, 183–194. [PubMed: 15010142]
- Klompén E, Engels T, Van Breemen L, Schreurs P, Govaert L, Meijer H, 2005 Quantitative prediction of long-term failure of polycarbonate. *Macromolecules* 38, 7009–7017.
- Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA, 1983 Mechanisms of solute release from porous hydrophilic polymers. *International journal of pharmaceutics* 15, 25–35.

- Krok A, Vitorino N, Zhang J, Frade JR, Wu C-Y, 2017 Thermal properties of compacted pharmaceutical excipients. *International journal of pharmaceutics* 534, 119–127. [PubMed: 29030289]
- Kumar A, Vercruyse J, Toiviainen M, Panouillot P-E, Juuti M, Vanhoorne V, Vervae C, Remon JP, Gernaey KV, De Beer T, 2014 Mixing and transport during pharmaceutical twin-screw wet granulation: experimental analysis via chemical imaging. *European Journal of Pharmaceutics and Biopharmaceutics* 87, 279–289. [PubMed: 24768925]
- Lakshman JP, Kowalski J, Vasanthavada M, Tong W-Q, Joshi YM, Serajuddin AT, 2011 Application of melt granulation technology to enhance tableting properties of poorly compactible high-dose drugs. *Journal of pharmaceutical sciences* 100, 1553–1565. [PubMed: 24081475]
- Lamoudi L, Chaumeil JC, Daoud K, 2016 Swelling, erosion and drug release characteristics of sodium diclofenac from heterogeneous matrix tablets. *Journal of Drug Delivery Science and Technology* 31, 93–100.
- Leane M, Pitt K, Reynolds G, Group MCSW, 2015 A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms. *Pharmaceutical development and technology* 20, 12–21. [PubMed: 25162770]
- Liu Y, Thompson M, O'Donnell K, 2018 Impact of non-binder ingredients and molecular weight of polymer binders on heat assisted twin screw dry granulation. *International journal of pharmaceutics* 536, 336–344. [PubMed: 29191485]
- Mahnaj T, Ahmed SU, Plakogiannis FM, 2013 Characterization of ethyl cellulose polymer. *Pharmaceutical development and technology* 18, 982–989. [PubMed: 21861778]
- Malkowska S, Khan K, Lentle R, Marchant J, Elger G, 1983 Effect of re-compression on the properties of tablets prepared by moist granulation. *Drug Development and Industrial Pharmacy* 9, 349–361.
- Mangal H, Kirsolok M, Kleinebudde P, 2016 Roll compaction/dry granulation: Suitability of different binders. *International journal of pharmaceutics* 503, 213–219. [PubMed: 26976499]
- Meijer HE, Govaert LE, 2005 Mechanical performance of polymer systems: The relation between structure and properties. *Progress in polymer science* 30, 915–938.
- Mohammed NN, Majumdar S, Singh A, Deng W, Murthy NS, Pinto E, Tewari D, Durig T, Repka MA, 2012 KluCel™ EF and ELF polymers for immediate-release oral dosage forms prepared by melt extrusion technology. *AAPS PharmSciTech* 13, 1158–1169. [PubMed: 22961411]
- Monteyne T, Heeze L, Mortier STF, Oldörp K, Cardinaels R, Nopens I, Vervae C, Remon J-P, De Beer T, 2016a The use of rheology combined with differential scanning calorimetry to elucidate the granulation mechanism of an immiscible formulation during continuous twin-screw melt granulation. *Pharmaceutical research* 33, 2481–2494. [PubMed: 27335024]
- Monteyne T, Vancoillie J, Remon J-P, Vervae C, De Beer T, 2016b Continuous melt granulation: Influence of process and formulation parameters upon granule and tablet properties. *European Journal of Pharmaceutics and Biopharmaceutics* 107, 249–262. [PubMed: 27449628]
- Narasimhan B, Peppas NA, 1997 Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier. *Journal of Pharmaceutical Sciences* 86, 297–304. [PubMed: 9050796]
- Nokhodchi A, Raja S, Patel P, Asare-Addo K, 2012 The role of oral controlled release matrix tablets in drug delivery systems. *BioImpacts: BI* 2, 175. [PubMed: 23678458]
- Nordstrom J, Alderborn G, 2015 The granule porosity controls the loss of compactibility for both dry- and wet-processed cellulose granules but at different rate. *Journal of pharmaceutical sciences* 104, 2029–2039. [PubMed: 25872760]
- Nystrom C, Alderborn G, Duberg M, Karehill P-G, 1993 Bonding surface area and bonding mechanism-two important factors for the understanding of powder comparability. *Drug development and industrial pharmacy* 19, 2143–2196.
- Plumb K, 2004 Major challenges for the pharmaceutical industry pharmaceutical industry in the new. *Pharmacia* 70, 1–32.
- Rajabi-Siahboomi AR, Bowtell RW, Mansfield P, Davies MC, Melia CD, 1996 Structure and behavior in hydrophilic matrix sustained release dosage forms: 4. Studies of water mobility and diffusion coefficients in the gel layer of HPMC tablets using NMR imaging. *Pharmaceutical research* 13, 376–380. [PubMed: 8692728]

- Russell A, Müller P, Tomas J, 2014 Quasi-static diametrical compression of characteristic elastic-plastic granules: energetic aspects at contact. *Chemical Engineering Science* 114, 70–84.
- Schulze S, Winter G, 2009 Lipid extrudates as novel sustained release systems for pharmaceutical proteins. *Journal of Controlled Release* 134, 177–185. [PubMed: 19121347]
- Stepani N, Milošević N, 2009 Correction on the influence of thermal contact resistance in thermal conductivity measurements using the guarded hot plate method. *Serbian Journal of Electrical Engineering* 6, 479–488.
- Sun CC, Himmelspace MW, 2006 Reduced tabletability of roller compacted granules as a result of granule size enlargement. *Journal of pharmaceutical sciences* 95, 200–206. [PubMed: 16315244]
- Tewari D, Durig T, 2014 Extrusion: An Enabling Technology for Controlled-Release Hydrophilic Matrix Systems, *Hydrophilic Matrix Tablets for Oral Controlled Release* Springer, pp. 233–255.
- Upadhye SB, ph Ronald SVR, Repka MA, Park J-B, TIWARI RV, Patil HG, MOROTT JT, Wenli L, 2017 Twin-screw dry granulation for producing solid formulations Google Patents.
- Vervaet C, Remon JP, 2005 Continuous granulation in the pharmaceutical industry. *Chemical Engineering Science* 60, 3949–3957.
- Walker G, Andrews G, Jones D, 2006 Effect of process parameters on the melt granulation of pharmaceutical powders. *Powder Technology* 165, 161–166.
- Wei Y, Nedley MP, Bhaduri SB, Bredzinski X, Boddu SH, 2015 Masking the bitter taste of injectable lidocaine HCl formulation for dental procedures. *AAPS PharmSciTech* 16, 455–465. [PubMed: 25361901]
- Wu CY, Bentham A, Mills A, 2007 Analysis of failure mechanisms during powder compaction, *Materials science forum*. Trans Tech Publ, pp. 237–240.
- Yalkowsky S, He Y, Jain P, 2010 *Handbook of aqueous solubility data* 2nd Edit. CRS Press, Boca Raton, FL ERDC/EL TR-17–8 ESTCP.
- Yun TS, Santamarina JC, 2008 Fundamental study of thermal conduction in dry soils. *Granular matter* 10, 197.
- Zhu Y, Shah NH, Malick AW, Infeld MH, McGinity JW, 2002 Influence of thermal processing on the properties of chlorpheniramine maleate tablets containing an acrylic polymer. *Pharmaceutical development and technology* 7, 481–489. [PubMed: 12503529]

Fig. 2.
Appearance of screw elements, II mixing zone & discharge elements, I mixing zone and barrel after removal of elements for unsuccessful (F18) (A, B, C and D) and successful (F1) granulation (E, F, G and H) trials.

Fig. 3.

(A) Physical mixture, (B) Twin-screw dry granules (before milling) and (C) Twin-screw dry granules (after milling).

Fig. 4. Particle size distribution studies of (A) Theophylline formulations, (B) APAP formulations and (C) LDH formulations (mean $\pm$ SD; n = 3).

Fig. 5. FTIR spectra of formulations, physical mixtures and APIs of (A) THP, (B) APAP and (C) LDH.

Fig. 6. DSC thermograms of formulations and respective APIs of (A) THP, (B) APAP and (C) LDH.

Fig. 7. XRD spectra of formulations, APIs, physical mixtures of (A) THP, (B) APAP, (C) LDH and (D) XRD spectra of all APIs.

Fig. 8. In-vitro drug release profiles of (A) T HP formulations, (B) APAP formulations and (C) LDH formulations (mean $\pm$ SD; n = 6).

Table 1

Formulations of THP, APAP and LDH prepared by twin-screw dry granulation.

Formulation code	M.P or Tg (°C)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Theophylline	272–274	50.0	50.0	50.0	50.0	50.0	50.0	-	-	-	-	-	-	-	-	-	-	-	-
Acetaminophen	169–171	-	-	-	-	-	-	40.0	40.0	40.0	40.0	40.0	40.0	-	-	-	-	-	-
Lidocaine HCl H ₂ O	82	-	-	-	-	-	-	-	-	-	-	-	-	30.0	30.0	30.0	30.0	30.0	30.0
Klucel™ MF	120	25.0	12.5	12.5	-	-	-	25.0	12.5	12.5	-	-	-	25.0	12.5	12.5	12.5	-	-
Aqualon™ 10 NF (EC)	150–156	-	-	12.5	12.5	12.5	25.0	-	-	12.5	12.5	12.5	25.0	-	-	-	-	-	-
Eudragit® RSPO	64–66	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12.5	12.5	12.5	25.0
Avicel® 102	260–270	24.8	37.3	19.8	27.3	22.3	5.0	34.8	47.3	29.8	37.3	32.3	19.8	-	-	-	-	-	-
Avicel® DG	260–270	-	-	-	-	-	-	-	-	-	-	-	-	44.8	42.3	29.8	34.8	37.3	24.8
Klucel™ EF	120	-	-	-	10.0	10.0	10.0	-	-	-	10.0	10.0	10.0	-	10.0	5.0	-	10.0	10.0
Kollidon® VA64	101	-	-	5.0	-	5.0	5.0	-	-	5.0	-	5.0	5.0	-	5.0	10.0	10.0	10.0	10.0
Magnesium stearate	148–152	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Table 2

Temperature settings of twin-screw granulation.

Temperature (°C)	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8
THP and APAP formulations	70	70	80	90	80	70	70
LDH formulations	45	55	55	55	55	45	45

Table 3

Process parameters of twin-screw granulation.

Formulation Code	% Drug load	% Feed rate (kg/h)	RPM	Granule formation	Torque (N-m) (Maximum torques equivalent to 12 N-m)
F1	50.0	0.176 – 0.293± 0.003	30–100	Yes	3.12–4.68
F2	50.0	0.174 – 0.295± 0.006	30–100	Yes	3.08–5.41
F3	50.0	0.171 – 0.285± 0.004	30–100	Yes	3.96–5.04
F4	50.0	0.176 – 0.294± 0.009	30–100	Yes	4.63–5.21
F5	50.0	0.173 – 0.291± 0.010	30–100	Yes	4.44–5.14
F6	50.0	0.171 – 0.287 ± 0.007	30–100	No	>12
F7	40.0	0.194 – 0.387± 0.004	30–100	Yes	2.64–4.08
F8	40.0	0.191 – 0.392± 0.006	30–100	Yes	3.84 –4.32
F9	40.0	0.189 – 0.388± 0.011	30–100	Yes	2.41–3.96
F10	40.0	0.190 – 0.385 ± 0.012	30–100	Yes	3.91–4.43
F11	40.0	0.192 – 0.381 ± 0.006	30–100	Yes	3.96–4.52
F12	40.0	0.188 – 0.387 ± 0.008	30–100	No	>12
F13	30.0	0.151 – 0.304± 0.006	30–100	Yes	2.76–3.82
F14	30.0	0.154 – 0.299± 0.004	30–100	Yes	2.85–3.94
F15	30.0	0.156 – 0.304± 0.008	30–100	Yes	2.84–3.88
F16	30.0	0.155 – 0.294± 0.004	30–100	Yes	2.91–3.86
F17	30.0	0.150 – 0.295± 0.004	30–100	No	>12
F18	30.0	0.152 – 0.297± 0.003	30–100	No	>12

Table 4

Granule properties produced by twin-screw granulation.

Formulation Code	% Drug load	Granule strength (g)	Granule stiffness (g/sec)
F1	50.0	2870.0±223.7	494.5±56.0
F2	50.0	2608.3±274.9	458.4±33.1
F3	50.0	2578.6±169.8	409.1±40.3
F5	50.0	2494.5±200.4	220.6±46.7
F7	40.0	2973.8±194.6	497.55±54.3
F8	40.0	2532.7±225.3	466.8±48.6
F9	40.0	2415.8±173.2	359.9±52.3
F11	40.0	2298.4±112.5	251.6±32.5
F13	30.0	3312.9±350.8	524.3±61.1
F14	30.0	3153.3±201.3	479.8±42.5
F15	30.0	2485.2±176.6	356.2±39.2
F16	30.0	2253.4±184.2	390.7±41.7

Table 5
Flow properties and evaluation parameters of tablets of twin-screw granulation formulations.

Formulation code	Angle of repose	Carr's Index (%)	Hardness (KP)	%Friability	Assay
F1	28.81 ± 0.45	15.1 ± 0.10	15.5 ± 1.14	0.10 ± 0.03	97.4 ± 1.24
F2	29.37 ± 0.91	15.7 ± 0.11	16.3 ± 1.24	0.15 ± 0.05	98.2 ± 1.45
F3	28.98 ± 0.74	14.9 ± 0.08	16.3 ± 1.05	0.21 ± 0.04	97.9 ± 1.68
F4	31.38 ± 0.65	16.3 ± 0.52	17.1 ± 1.11	0.23 ± 0.05	100.3 ± 1.55
F6	29.68 ± 1.11	17.1 ± 0.90	15.3 ± 0.84	0.15 ± 0.06	99.4 ± 2.32
F7	30.11 ± 0.98	15.9 ± 1.10	16.5 ± 0.91	0.17 ± 0.04	98.9 ± 2.05
F8	30.96 ± 0.57	16.1 ± 1.14	16.8 ± 0.65	0.34 ± 0.03	101.3 ± 1.12
F9	29.46 ± 0.99	15.4 ± 0.82	15.1 ± 1.32	0.29 ± 0.03	102.1 ± 1.34
F11	30.71 ± 0.21	16.4 ± 0.67	16.4 ± 1.06	0.19 ± 0.07	101.5 ± 1.41
F12	29.42 ± 0.35	14.8 ± 0.11	16.5 ± 0.59	0.20 ± 0.09	103.2 ± 1.14
F13	28.72 ± 0.54	16.2 ± 1.13	16.8 ± 0.88	0.31 ± 0.03	100.6 ± 2.14
F14	28.41 ± 1.16	13.4 ± 1.26	15.9 ± 1.20	0.33 ± 0.04	98.8 ± 1.93

Table 6

Release kinetics of formulations of twin-screw granulation.

Formulation code	Zero order	First order	Correlation coefficient (R ²)		Diffusional Exponent (n)
			Higuchi	Korsmeyer-Peppas	
F1	0.9024	0.6918	0.9748	0.9751	0.477
F2	0.9742	0.8574	0.9914	0.9941	0.484
F3	0.966	0.8582	0.9885	0.9850	0.476
F5	0.9578	0.8583	0.9782	0.9918	0.553
F7	0.8030	0.6543	0.9726	0.9361	0.821
F8	0.9027	0.8685	0.9533	0.9981	0.524
F9	0.825	0.7343	0.9116	0.9427	0.476
F11	0.7784	0.7072	0.8819	0.9734	0.462
F13	0.7819	0.671	0.9154	0.9852	0.481
F14	0.8507	0.6983	0.9581	0.9942	0.590
F15	0.9569	0.8414	0.9761	0.9225	0.674
F16	0.9512	0.8351	0.9728	0.9450	0.802