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Selected abstracts from Excipient Fest 2017

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Preface

The International Pharmaceutical Excipients Council (IPEC) is the global association of manufacturers and users of pharmaceutical Excipients. Each year, ExcipientFest Americas brings together a global community of Pharmaceutical Scientists for a unique two-day forum focused on the latest scientific research and developments for pharmaceutical excipients. The meeting combines in-depth technical talks on Excipient Technology, New Drug Applications, and Regulatory Issues from the industry's top-pharmaceutical experts. Students, Professors, and Industry Professionals are invited to present posters at ExcipientFest Americas on topics related to Excipient Technology or Drug Application. The poster presentations are peer evaluated, and we are pleased to present their associated abstracts here in this special focus section, enjoy!

Please use the following link to find out more about the upcoming ExcipientFest Americas meeting in San Juan, Puerto Rico, 2018: http://www.excipientfest.com/

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Effect of drug concentration on viscosity of submicron dispersions of coenzyme Q10

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The aim of this study was to formulate self-emulsifying coenzyme Q10 (CoQ10) systems that could be suitable for aerosolization. CoQ10, is a vitamin-like compound that is a poorly water soluble. CoQ10 is being widely investigated for use in cardiac disease, lung fibrosis, as well as cancer therapeutics. This potentially anti-cancer agent is naturally present in most eukaryotic cells, it predominantly aids electron transport and proton transfer in mitochondrial respiration. In this work, aqueous submicron emulsions of CoQ10 for pulmonary delivery were formulated using appropriate amounts of non-ionic stabilizers (polysorbate 80:Capryol 90) and a co-solvent (triglyceride of coconut oil), followed by high-shear homogenization. Particle sizes (*z*-average) and viscosities were evaluated with respect to drug concentration and emulsion composition. It was observed that, by varying the concentration of surfactant, the interfacial tension between the oil and water varied. Lesser concentrations of surfactant resulted in unstable emulsions, and phase separation was seen. The self-emulsifying water in oil emulsions were prepared using drug concentrations of 0.1, 0.3, 0.5% w/v in 95% water (with the balance being emulsifiers/co-solvent). The *z*-average values of these emulsions were observed to be approximately 186, 293.5, and 330 nm, respectively. By rheological analysis, the magnitude of shear stress was found to be inversely related to the particle size. It was noted that the emulsions with lower drug concentrations and increasing surfactant concentration demonstrated increased shear rate, thereby reducing the overall viscosity of the emulsions. The average viscosity of the emulsions ranged from approximately 3.5 to 6.8 centipoise. In conclusion, it can be confirmed that any anticipated submicron particle size reduction of the emulsion, may be appropriately attributed to changes in rheological properties that are a consequence of varying surfactant concentration, as well as CoQ10 concentrations.

Effect of co-processed spray dried sodium alginate and dibasic calcium phosphate on drug release characteristics

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Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid. In tablet formulations, sodium alginate may be used as both a binder and disintegrant. In high concentrations (60–90% w/w), it is also incorporated in matrix tablets for the retardation of drug release. Previous research has described tablets containing sodium alginate, prepared using wet granulation techniques. However, its non-uniform particle size, poor flow properties, high-loading requirement, and poor compressibility does not make it an excipient of choice for direct compression tableting, or oral controlled drug delivery systems. Co-processing may offer a suitable alternative to mitigate some of the aforementioned formulation difficulties. In this study, sodium alginate was co-processed with dibasic calcium phosphate (DCP) in the weight ratio of 1:1, 1:2, or 2:1 via spray drying. The co-processed spray dried sodium alginate was characterized using scanning electron microscopy (SEM), and differential scanning calorimetry. Venlafaxine hydrochloride and diclofenac sodium were chosen as model drugs, to study the effect of spray dried co-processed sodium alginate on drug release from tablet formulations. Spray drying of sodium alginate with DCP rendered it spherical with uniform particle size, improving its flow properties and compressibility; presenting as a ready-to-use directly compressible excipient. Most importantly it imparted enhanced sustained release

properties, while allowing for a low quantity of co-processed sodium alginate (17% w/w) required for tableting, even for a highly soluble drug like venlafaxine hydrochloride. Maximum sustained release properties were found with 2:1 ratio of sodium alginate: DCP. In addition, the burst release of drugs was also reduced using the co-processed material, compared to a conventional tableted formulation type.

Manufacture and assessment of a novel 3D printed induction port for cascade impactor analysis

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The aim of this study was to develop a novel 3D printed aerosol induction port (IP) based on physiological conditions, for use with a standard cascade impactor that could be used to improve *in vitro/in vivo* correlation (IVIVC) of aerosolized medications. The IP, used for aerosol classification with USP apparatus 5, as monographed in the USP (USPIP) lacks physiological accuracy, leading to poor predictability of *in vivo* lung deposition of pharmaceutical aerosols from *in vitro* experiments. A modified IP (mIP) was prepared using a 3D model of a human trachea that was extracted from a computer tomographic dataset, cleaned up, merged with adaptor fittings, and printed using a X400 3D printer. To evaluate the influence of the printing material a polymeric copy (USPIP3D) of the USPIP was manufactured. Test objects were assessed by analysis of the aerodynamic properties of commercially available salbutamol (SAL) formulations. Here we present results obtained analyzing a binary dry powder formulation Ventilastin®, dispensed from the Novoloizer® dry powder inhaler. A next generation cascade impactor (NGI) was operated at a pressure drop over the inhaler of 4 kPa. Ten actuations of 100 µg SAL each, were dispensed into the NGI. Samples were analyzed using a validated HPLC method. SAL powder analyzed using the USPIP showed a deposition of 27.9 ± 3.1%. Mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and fine particle fraction (FPF) were found to be 1.69 ± 0.05 µm, 2.85 ± 0.11, and 27.57 ± 1.19%, respectively. The mIP showed a particle deposition of 31.5 ± 6.1%. MMAD, GSD, and FPF were found to be 1.89 ± 0.13 µm, 2.74 ± 0.16, and 24.1 ± 4.99%, respectively. In conclusion, the USPIP3D performed statistically equivalent to the USPIP, and a physiologically relevant IP that could be used to yield a better IVIVC of lung deposition was successfully manufactured and evaluated.

Investigating the effect of magnesium stearate hydrate form on tablet dissolution

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This work focuses on understanding magnesium stearate (MgSt) lubrication, by studying the effects of the hydrate forms of MgSt on tablet dissolution. MgSt is ubiquitous in the pharmaceutical manufacturing industry as a powder lubricant; however, the variability from batch to batch and vendor to vendor can lead to large inconsistencies in terms of lubrication. A better understanding of the relationship between the molecular properties and functional properties of MgSt will allow improvements to be made, in terms of tablet manufacturing. MgSt samples were synthesized by two processes: (i) a bath synthesis method produced variations of pure dihydrate and mixtures of monohydrate, dihydrate and trihydrate, depending on the conditions and MgSt to magnesium palmitate ratio; (ii) a melt method predominantly made MgSt monohydrate. These materials were blended into formulations using a blend of 1 or 2% w/w MgSt with indomethacin, MCC, and lactose. A turbula mixer was used to blend the formulations for a series of discrete time points between 1–60 min, at which time tablets were produced at two distinct compressive forces using a single-punch tablet press. Dissolution was performed on the tablets using a USP apparatus 2, equipped with UV fiber optic probe detection. Significant differences in dissolution were observed between tablets prepared with the different hydrate forms, in particular, tablets containing MgSt trihydrate consistently showed slower dissolution. As expected, longer mixing times slowed dissolution, and higher compression forces appeared to slow disintegration of the tablets containing MgSt. In conclusion, synthesis methods were developed enabling the production of pure monohydrate, pure dihydrate, and hydrate mixtures of MgSt. In addition, a mixing/tableting/dissolution procedure was developed which was able to distinguish between tablets containing different hydrate forms of MgSt. Furthermore, differences in mixing time as well as compression force correlated with differences in dissolution.

Cleaning validation life cycle approach

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Oral solid dose products contain one or more active components as well as numerous excipients used as fillers, disintegrating agents, binding agents, lubricants, colorants and/or coatings. The broad diversity of actives, excipients, and product variations make it difficult for manufactures to design a single cleaning strategy. The presented work will provide an overview of the life-cycle approach to cleaning validation for product contact surfaces of equipment. The three phases of life cycle approach: cleaning development, cleaning qualification, and cleaning monitoring will be discussed including how they contribute to a compliant, evolving cleaning program. The cleaning development design phase takes the cleaning assessment and develops a protocol describing any needed cleaning development activities, including critical quality attributes and critical process parameters for the proposed cleaning procedure. The cleaning qualification phase takes documented evidence through an executed protocol which provides a high degree of assurance that a cleaning procedure consistently removes residues to predetermined, acceptable levels; and the cleaning procedure process capability parameters can be established to provide ongoing assurance that the cleaning procedure remains in a state of control. The cleaning monitoring phase takes documented evidence that the validated cleaning program remains in a state of control. Annual document review including: non-conformances and change control are used to evaluate whether the cleaning procedure under review continues to be effective and has not undergone changes that might impact the validated state.

Synergistic effects of three functional excipients in a tablet

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The purpose of this work was to produce rapidly disintegrating yet strong tablets by finding the optimum balance of excipients: Pharmacel® 102 microcrystalline cellulose (MCC), SuperTab® 24AN anhydrous lactose (Lac), and SuperStarch® 200, a partially pregelatinized starch (PPS). Maximum tensile strength, minimum friability, and disintegration times were used as factors to optimize excipient usage. A three component matrix was developed and experimental design points, with a maximum 50% w/w constraint on PPS. Placebo tablets were prepared at 4 kN compaction force for each blend, and tested for friability, tensile strength, and disintegration time. Results were evaluated using Box–Cox transformation, due to a non-normal distribution of responses. The logarithm of tensile strength and friability, and the square root of disintegration time were calculated and analyzed using Minitab v 16; according to a mixture design with a step wise regression approach, in order to remove insignificant factors ($p > 1.25$). As with all tablet formulations, multiple excipients are mixed to achieve a desired final product (e.g. tablet or capsule). A mixture is used as each component has specific role to play that is dependent upon physical properties like elasticity or brittleness. Granulated anhydrous Lac brings brittleness and flow to a formulation; MCC brings elasticity and tablet strength; while partially PPS brings elasticity and binding force to the formulation; in addition, MCC and PPS facilitate the disintegration of tablets. The significance levels (p-values) of significant terms between components was evaluated, and the tensile strength profile of the mixture design was determined. Lac and MCC were seen to provide strength and low friability to the tablet; the weakest tablets were seen at high-PPS levels. Notably, above 25% w/w MCC, friability was <0.5% w/w. A more complex pattern was observed for disintegration time, with the fastest disintegration not found at 100% pure compositions. Due to synergy of the individual components, the optimum tablet blend was found for equal amounts of MCC and Lac (45:45% w/w) with a small amount of PPS (approximately 10% w/w). Although 100% MCC tablets have the lowest friability and highest tensile strength, synergy in disintegration time is found by blending in Lac and PPS. In conclusion, this work may provide formulation knowledge by providing an understanding of the interaction between each of the three functional excipients used. The formulation design approach used recognized a synergy that led to the identification of suitably hard tablets, with low friability, and low disintegration times.

Robustness studies of drug release from sustained-release matrix tablets using hypromellose QbD sample kit

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In this study, the effects of hydroxypropyl methylcellulose (HPMC) properties on robustness of drug release were investigated using quality by design (QbD) principles. When hydrophilic matrix tablets are prepared using hypromellose (a,k.a. HPMC), the hydration behavior of HPMC is one of the critical attributes for drug dissolution. The hydration behavior is affected by the viscosity, chemical substitution level such as hydroxypropoxy (HPO) content, and HPMC particle size. In accordance with an ICH guideline, implementation of QbD principles to formulation development is strongly recommended. QbD often leads to an understanding of how the properties and performance of the dosage forms are influenced by the formulation, including the quality attributes of HPMC. A sample kit of METOLOSE® SR HPMC with high to low levels of hydroxylpropoxy content, viscosity, and particle size was prepared by modification of processing parameters in its reaction and further downstream process. The sample kits with the same design were prepared for four commercially-available viscosity grades of HPMC: (i) 90SH-100SR (100 mPa·s), (ii) 90SH-4000SR (4000 mPa·s), (iii) 90SH-15000SR (15,000 mPa·s), (iv) 90SH-100000SR (100,000 mPa·s). Several APIs including dipyridamole, acetaminophen, and metformin were used for release indicator to test robustness of drug release using the HPMC samples. In most cases in the study the drug release did not show significant difference as long as the same viscosity grade was used, but some effect by HPO content was seen. In conclusion, the sample kit used in this study was found to be useful for QbD applications investigating the effect of hydration behavior in various HPMC viscosity grades.

Effect of drying methods on the powder and compaction properties of microcrystalline cellulose (MCC) derived from *Gossypium herbaceum* (GH)

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The effect of a process variable drying method on the compaction properties of microcrystalline cellulose (MCC) obtained from the partial acid hydrolysis of alpha cellulose content of *Gossypium herbaceum*, was investigated. Two drying methods were used: fluidized bed drying (at 60 ± 1 °C, inlet air of 30 m^3 per minute for 3 h) and lyophilization (at −45 ± 2 °C for 6 h). The fluidized bed dried and lyophilized MCC were coded MCC-FD and MCC-LF, respectively. The physicochemical properties of the derived MCCs, scanning electron micrographs, and X-ray diffraction patterns were determined using standard methods. The compaction properties were assessed using the Kawakita and Heckel analysis models. Results showed ash values <2%, pH 6.54–6.58, and swelling capacities of 118.01 and 97.20% w/w for MCC-FD and MCC-LF, respectively. MCC-FD had a higher moisture content, better flow index, and a lower porosity than MCC-LF. Both MCCs demonstrated good consolidation and compactibility. Compacts of MCC-LF were significantly harder than that of MCC-FD ($p < .05$). Heckel analysis showed good compressibility and a deformation pattern that was comparable with Avicel® PH 102. The MCC-LF exhibited better reworking potential than the MCC-FD. The scanning electron microscopy of MCC-FD and MCC-LF were consistent with microcrystalline cellulose fibers. In summary, the overall results showed that method of drying significantly affected the powder and compaction properties of MCC derived from GH ($p < .05$). In addition, lyophilized MCC produced compacts that had better mechanical and tablet compression properties than the fluidized bed dried MCC.

Improved dissolution behavior of poorly soluble drug in hydrophobic matrix with novel dissolution initiator utilizing melt extrusion technology

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The purpose of this study was to understand the behavior of pregelatinized hydroxypropyl pea starch polymer (Lycoat® RS 780) as a dissolution initiator, for drug release improvement of clotrimazole from ethyl cellulose (EC) formulated by hot melt extrusion (HME). Thermogravimetric analyses (TGA) were performed using a Perkin Elmer Pyris 1 TGA on EC, clotrimazole, and Lycoat® RS 780 to evaluate thermal stability at the employed extrusion temperatures. Clotrimazole (20% w/w) and EC were mixed with and without Lycoat® RS 780 (20 or 40% w/w) using a V-shell blender. A plasticizer, either triethyl citrate (TEC) or stearic acid, was used to improve the processability of hydrophobic matrices during HME. The blends were extruded using a ThermoFisher Scientific 16 mm Prism EuroLab twin-screw extruder, at screw speeds of 100 rpm and over a temperature range of 145–150 °C. The extrudates were milled and sieved using a Fitzpatrick model L1A comminuting mill. The physical characteristics of the API and extrudates were confirmed by differential scanning calorimetry (DSC). Milled extrudates were studied for *in vitro* release in 1% w/v sodium lauryl sulfate dissolution medium using a Hanson SR8 USP Type-II apparatus at 37 ± 0.5 °C, and 50 rpm. Samples collected at various time intervals were analyzed using a validated HPLC method. Clotrimazole, EC, and Lycoat® RS 780 demonstrated good compatibility, which was reflected in thermal stability and suitability for the melt extrusion process. As plasticizers, TEC and stearic acid aided in processing improvement during the HME. DSC thermograms of extruded formulations, exhibited the loss of API associated crystalline peaks, confirming the crystalline to amorphous transition of clotrimazole. Dissolution profiles of formulations with Lycoat® RS 780 displayed a significantly higher rate and extent of clotrimazole release from the polymeric matrix (two-fold increase after 30 min, and three-fold increase after 60 min) compared to Lycoat® RS 780 free formulations. This study confirmed the potential of Lycoat® RS 780 to act as a dissolution initiator, improving drug release from ethylcellulose hydrophobic matrices formulated using HME.

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Zaleplon microparticles delivery in patient centric drug delivery systems (oral disintegrating tablets and oral dissolving film)

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The present research focused on zaleplon (a BCS class II drug) micronization, and enhancement of its oral delivery by orodispersible tablets (ODTs), or orodispersible films (ODFs) using novel formulation platforms Pearlitol Flash® and Lycoat® RS720, respectively. A known amount of zaleplon powder was mixed with a surfactant solution. After high-speed homogenization, the suspension was broken down using an ultrasound probe, before lyophilization. Micronized zaleplon powder was characterized for particle size distribution, crystallinity, drug content, and dissolution. Zaleplon ODTs were formulated by direct compression on a Korsch XP1 tablet press using the ODT platform, Pearlitol Flash® The API content analysis and disintegration time was evaluated using standardized USP methods. The film suspension was prepared at room temperature by adding LYCOAT® RS720 to an aqueous plasticizer solution, followed by the addition of a zaleplon microparticle suspension. The zaleplon mixture was emulsified under continuous mixing for approximately 15 min. The films were cast using RK Control equipment and dried at 25 °C/60% RH, before being cut into $3 \times 2\,cm^2$ strips. The ODF was evaluated using optical microscopy, Fourier transform infrared spectroscopy, and texture analysis. Micronization reduced the particle size of crystalline drug by approximately six-fold, when compared to its original particle size of 155.5 μm. The particle size analysis and *in vitro* dissolution study showed that micronized zaleplon displayed greater dissolution behavior due to increased surface area for dissolution. Desirable hardness and a smooth texture for the ODT units, was attributed to the usage of Pearlitol Flash® as a pre-prepared ODT platform product. In addition, good tensile strength was observed for ODFs loaded with micronized zaleplon and prepared with Lycoat® RS 720. The disintegration time of ODTs and ODFs was 30 ± 5 and 35 ± 5 s, respectively. In conclusion, the orodispersible formulations containing micronized zaleplon displayed rapid disintegration; potentially ensuring good systemic absorption via the oral cavity.