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The Effects of Screw Configuration and Polymeric Carriers on Hot-Melt Extruded Taste-Masked Formulations Incorporated into Orally Disintegrating Tablets

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Abstract

The primary aim of this research was to produce successfully taste masked formulations of Sildenafil Citrate (SC) using hot-melt extrusion (HME) technology. Multiple screw configurations and polymeric carriers were evaluated for their effects on taste masking efficiency, which was assessed by both E-tongue analysis and *in vitro* dissolution in simulated salivary fluid (SSF, pH 6.8 artificial saliva). The screw configurations were further assessed for their effects on the morphology of the API using PXRD, FT-IR and mid-infrared chemical imaging. It was determined that the screw configuration had a profound effect on the taste masking efficiency of the formulations as a result of altering the physical state of the API. Selected extruded formulations using ethylcellulose (EC) with a pore former were further formulated into orally disintegrating tablets (ODTs), which were optimized by varying the grade and percentage of the superdisintegrant used. An optimized disintegration time of approximately 8 seconds was achieved. The final ODT formulation exhibited excellent taste masking properties with over 85% drug release in gastric media as well as physical tablet properties. Interestingly, friability, which tends to be a common concern when formulating ODTs, was well within the acceptable limits (<1%) for common tablets.

Keywords

Hot Melt Extrusion; Taste Masking; Crystalline Solid Dispersion; Bitter API; Disintegrating Tablets; Chemical Imaging; Screw Configuration

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1. INTRODUCTION

The perception of taste, or palatability, of a pharmaceutical dosage form is a significant concern in terms of patient compliance. The development of successfully taste-masked formulations remains to be a particularly formidable challenge when formulating oral dosage forms for pediatric populations, who actively refuse to ingest drugs with an unpleasant taste, and/or geriatric populations, who tend to exhibit unique perceptions of taste.[1, 2] A 2003 survey of Pediatricians conducted by the American Association of Pediatrics concluded that the unpleasant taste of oral dosage forms was the single greatest obstacle in completing a prescribed therapy due to a lack of patient compliance.[1] This problem is further accentuated when attempting to formulate orally dissolving/disintegrating platforms (i.e. dissolvable films, orally disintegrating tablets, etc.) wherein more traditional methods of taste-masking, such as tablet film coating, are not feasible. These rapidly dissolving platforms have received considerable attention as they do not require equipment for dosing (oral syringes, measuring cups, etc.), chewing or additional liquids in order to be administered. This is because these dosage forms are intended to completely dissolve or disintegrate utilizing only the saliva available in the oral cavity. While convenient for all populations, this quality makes them ideal for patients who suffer from dysphagia, which is common in both pediatric and geriatric populations, where patient compliance is an issue (i.e. psychiatric disorders, etc.), or for chronic conditions that are characterized by random and rapid onset such as anxiety attacks or migraine headaches.[3-8] Unfortunately, ODTs tend to be relatively fragile and suffer from increased friability which, in turn, leads to more expensive packaging requirements.

Sildenafil Citrate (SC), a phosphodiesterase type 5 inhibitor with a markedly bitter taste, has been marketed to both pediatric and geriatric populations as Revatio®, for the treatment of pulmonary arterial hypertension, and Viagra®, for the treatment of erectile dysfunction, respectively.[9-12] As a BCS I drug, SC presents an additional difficulty in terms of taste masking as it readily goes into solution while in the oral cavity thereby allowing it to interact with taste receptors more rapidly. Moreover, SC is used to treat the aforementioned chronic conditions which necessitate repeated exposure to the drug and excipients used in these formulations. This is a particular concern in both pediatric and geriatric populations where a heightened sensitivity to even the most modest toxicity may exist.[13,14]

Hot-melt extrusion has emerged as a novel and appealing pharmaceutical processing technology in recent years.[15] HME processes are characterized by the pumping of raw materials along a rotating screw, or screws, inside a barrel at elevated temperatures. The molten material is then forced through a die into a substance of uniform shape and character where it is then collected for further use.[16] HME is an attractive processing option for pharmaceutical applications as it is a potentially continuous process, does not necessitate the use of water or toxic organic solvents, is easily scaled up, provides relatively short processing times, and many of the polymeric carriers employed during processing are generally recognized as safe.[16,17] This technology is best recognized for its ability to enhance the solubility of poorly water soluble APIs; however, it can also be extended to BCS I compounds in which solubility enhancement is not required.[18] This application is explored in this research through the modification of screw configurations for the purpose of

maintaining the API's crystallinity while also achieving acceptable homogeneity in the extrudates. Here, three configurations and their effects on the physical state of SC are investigated.

To be suitable for taste masking applications, however, the selected polymeric carrier must have two qualities. First, it must inhibit interaction of the API with taste receptors in the mouth. Second, it must not prevent dissolution in the GI tract. Successful taste masking via HME technology would minimize both ensuing processing steps as well as the quantity of flavor enhancing excipients required to produce an acceptable tasting end product. In this current research, Plasdone™ S-630 copovidone, Aqualon™ N7 ethylcellulose (EC) and multiple grades of Klucel™ (HF, EF & ELF) hydroxypropylcellulose (HPC) polymers, were evaluated for their effectiveness in taste masking. The most suitable of the polymeric carriers, ethylcellulose, as evaluated by taste masking efficiency, was selected for additional experimentation and ultimately for formulation into an ODT.

2. MATERIALS AND METHODS

2.1 Materials

Copovidone (Plasdone™ S-630), hydroxypropylcellulose (Klucel™ ELF, EF, & HF), ethylcellulose (Aqualon™ N7), Polyplasdone™ XL & XL-10 and Sildenafil Citrate were kindly gifted by Ashland Specialty Ingredients (Wilmington, DE). Mannitol (Pearlitol™ 300-DC) was donated by Roquette America Inc. (Keokuk, IA). Sucralose was gifted from JK Sucralose (Jiangsu Provence, China). Monoammonium Glycyrrhizinate (Magnasweet®) was donated by Mafco Worldwide CORP. (Camden, NJ). Butylated hydroxytoluene (BHT) was purchased from Sigma-Aldrich (St. Louis, MO). Magnesium Stearate was purchased from Spectrum Laboratory Products Inc. (Gardena, CA.). Calcium carbonate, magnesium oxide, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium chloride, potassium carbonate, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate as well as all solvents used in these studies (analytical grade methanol, acetonitrile & water), were purchased from Fisher Scientific (Norcross, GA). Natural & artificial mint flavoring was gifted by Flavors of North America (Carol Stream, IL).

2.2 Hot-Melt Extrusion

2.2.1 Thermogravimetric (TGA) & Differential Scanning Calorimetry (DSC) Analysis—TGA (Pyris 1 TGA Perkin Elmer) was utilized to determine the thermal stability of the individual polymers, BHT, mannitol, magnesium oxide, calcium carbonate and pure SC. Binary mixtures (1:1 w/w) of the individual excipients with SC, as well as complete physical mixtures, were examined at the temperatures required for melt extrusion processing. During TGA, each of the weighed samples was heated from 25°C to 180°C at a rate of 20°C/min. in a platinum pan under an inert nitrogen atmosphere purge of 20ml per minute. The samples were held at 180°C for 5 minutes to simulate the thermal stresses encountered during HME.

DSC (Diamond DSC, Perkin Elmer) was utilized to confirm the thermal stability of replicate TGA samples. The samples, weighing 4-5 mg each, were placed in hermetically sealed

aluminum pans and placed under an inert nitrogen atmosphere at a purge rate of 20ml per minute. These samples were heated from 25°C to 180°C at a rate of 20°C/min., held at 180°C for 5min. and cooled to room temperature. The thermograms of the samples were analyzed for deviations from samples of the pure substances, as well as for other thermal events. Calibration of the instrument was performed with an Indium reference.

2.2.2 Hot-Melt Extrusion Processing—Prior to HME processing, the polymers were sieved with a USP #35 mesh screen to remove any aggregates that may have formed. The compounds necessary for each physical mixture (table 1) were placed in a V-shell blender (GlobePharma, Maxiblend®) and mixed at 20 rpm for 20 minutes. API content uniformity in the physical mixtures was assessed by HPLC analysis using a Waters HPLC-UV system (Waters Corp, Milford, MA). A fully intermeshing co-rotating twin-screw extruder (11 mm Process 11™, ThermoFisher Scientific) was used to process the physical mixtures. The barrel temperature profile and screw speed were based on the physical properties of polymeric carrier in each of the preliminary physical mixtures (Table 1) and a 2mm rod die was attached to the end of the barrel. Three screw configurations were investigated for their effects on the physical state of SC post extrusion (Figure 1a-c).

After allowing the extruder to reach a steady state, material was collected from the extruder as uniform cylindrical extrudates. The extrudates were allowed to cool to ambient temperature and stored in foil lined polyethylene bags for further processing. The extrudates were later milled using a comminuting mill (Fitzpatrick, Model L1A). The milled extrudates were sieved to a particles size range of 300-425μm using what was retained between US #35 and US #40 sieves. The milled and sieved extrudates were stored in glass vials with a foil lined cap for future use.

2.2.3 Post-Processing Drug Content—A randomly selected portion of each of the extruded formulations was crushed into a fine powder using a mortar & pestle and analyzed for post-extrusion drug content. A known amount of the extruded formulations was dissolved in 1:1 methanol:water, diluted with additional 1:1 methanol:water and filtered using 0.2 μm, 13 mm PTFE membrane filters (Whatman, Piscataway, NJ) and analyzed using HPLC analysis. The same method was used to evaluate the finished ODT formulations.

2.2.4 HPLC Analysis—The SC content in dissolution samples was analyzed using a Waters (Waters Corporation, Milford, MA, USA) high performance liquid chromatography (HPLC) system equipped with an autosampler, UV detector and a Phenomenex® Luna 5μ C18 (150 × 4.6 mm) column. An isocratic mode of elution with a mobile phase consisting of acetonitrile and water (60:40) at a flow rate of 1.0ml/min. was employed to quantify the drug at a wavelength of 273 nm. The data was acquired and processed using Waters Empower 3 software suite.[19]

2.2.5 PXRD Analysis—Powder X-Ray Diffraction (Bruker AXS, Madison, MI) was utilized to determine the physical state of SC post extrusion. The X-ray diffraction apparatus used CuKα radiation at 35 mA and 40 kV, 2°/min, and diffraction angles (2θ) of 5-50.

2.2.6 FT-IR & Mid Infrared Chemical Imaging—Mid infrared spectral analysis was conducted on an FT-IR bench (Agilent Technologies Cary 660, Santa Clara, CA.). The bench was equipped with an ATR (Pike Technologies MIRacle ATR, Madison, WI), which was fitted with a single bounce diamond coated ZnSe internal reflection element. Chemical imaging was conducted using an infrared microscope (Agilent Technologies Cary 620 IR, Santa Clara, CA.) equipped with a 64 × 64 pixel focal plane array (FPA) with and without a germanium micro-ATR.

2.2.7 Dissolution Testing of Milled Extrudates—The milled and sieved extrudates were tested for *in vitro* drug release in both 150ml of SSF (pH 6.8 artificial saliva, Table 2) and 900ml of pH 2 media (0.01N HCl) with USP apparatus I (Hanson SR8) at 37 ± 0.5°C with a rotation speed of 100 rpm (n=6).[20,21]

2.2.8 Preformulation for Tableting—Binary (1:1 w/w) mixtures of the milled extrudates with each of the excipients employed for tableting, as well as complete physical mixtures representative of the final tablet formulations, were stored under accelerated stability conditions (40°C ± 2°C/75% RH ± 5% RH) for one month. These samples were then qualitatively analyzed by FT-IR and quantitatively analyzed by HPLC.

2.2.9 Tablet Compression—Prior to direct tablet compression, the milled extrudates were mixed with mannitol, sucralose and Monoammonium Glycyrrhizinate in a V-shell blender at 20 rpm for 20 min. Magnesium Stearate was added during the last 2 minutes of blending. The API content uniformity was determined by HPLC analysis. ODTs were prepared on a ten-station Piccola tablet press (SMI) using 8.0 mm standard concave tooling and a compression force of 5.5 kN.

2.2.10 Tablet Properties (Friability, Hardness, Disintegration & Weight Variation)—A dual scooping projection Vanderkamp friabilator (Vankel Industries Inc. Chatham, NJ) filled with 22 300mg ODTs in one side, to meet USP requirements, was used to assess tablet friability. The friabilator, which rotates at 25 rpm, was allowed to rotate continuously for four minutes. The tablets were accurately weighed prior to the test, and carefully de-dusted and reweighed after the test.

Tablet hardness was assessed using a Schleuniger hardness tester. Each tablet tested was placed firmly against the stationary anvil prior to beginning the test, and all debris from the previous test was carefully removed before performing replicate tests (n=10).

Weight variation was measured on a microbalance. 20 tablets were weighed, and their average determined. The weight of the individual tablets was then compared to the average and evaluated within USP specified tolerances for uncoated tablets (± 7.5%).

Tablet disintegration time was measured on a disintegration tester (Dr. Schleuniger Pharmatron). The beakers were filled with one liter simulated salivary fluid (pH 6.8 buffer solution, Table 2). The unit was thermally equilibrated to 37 ± 2°C (n=6) prior to tablet disintegration testing. Each tube of the apparatus was used to hold one tablet and each tablet was covered with a perforated plastic disc. The test was concluded when no particles were

retained by the 10-mesh in the bottom of each tube. Prior to beginning the test, it was determined that the basket oscillations were between the recommended 28-32 cycles per minute.

2.2.11 Electronic Tongue Analysis—The electronic tongue samples were assayed on an Astree e-tongue (Alpha M.O.S.) equipped with sensor set #2 (pharmaceutical analysis) composed of seven sets of sensors (ZZ, AB, BA, BB, CA, DA, & JE) on a 48 position auto sampler. The individual sample volumes were 25ml and the acquisition times were set at 120s. The data generated on the e-tongue was analyzed using principle component analysis on the AlphaSoft V12.3 software suite (Mathworks Inc., Massachusetts, USA). Each sample was run at least three times, and three replicates of these samples were utilized for statistical purposes. The sensors and sample containers were thoroughly cleaned with deionized water between each sample assay. The individual assayed samples were diluted for 60 seconds in 25 ml of phosphate buffer solution (pH 6.8) in order to simulate oral conditions, and the supernatant liquid was filtered through 2.5 μm syringe filters.

2.2.12 ODT Oral & Gastric Tablet Dissolution—*In vitro* oral drug release was measured using dissolution apparatus I (Hanson SR8) set to 100 rpm and equipped with UV-Vis probes (Rainbow Dissolution Monitor, pION) collecting every 5 seconds for 60 seconds at 273nm. The dissolution medium consisted of SSF (150ml of artificial saliva pH 6.8, Table 2) and was maintained at 37 ± 0.5°C (n=6). *In vitro* gastric release was evaluated using dissolution apparatus I (Hanson SR8) set to 100 rpm. The dissolution medium consisted of 0.01N HCl (900ml) and the temperature was held at 37 ± 0.5°C. Samples were collected at 5, 10, 15 & 30 minute time points (n=6).

2.2.13 Physical and Chemical Stability—The final ODT formulations, as well as milled extrudates containing the API, were stored under standard (25°C/65% RH) and accelerated (40°C/75% RH) stability conditions for 6 months in unclosed glass containers. The dissolution similarity factor (f_2) was utilized to compare the post-stability dissolution profiles of the ODTs. The milled extrudates were utilized for physical stability analysis of the API.

2.2.14 Statistical Analysis of Dissolution Data—The dissolution data, whether collected using Uv-Vis probes (section 2.2.12), or more conventional HPLC analysis (section 2.2.4, 2.2.7 & 2.2.12), were subjected to statistical analysis using the Similarity Factor (f_2) which allows for an accurate comparison of immediate release dissolution profiles.

3. RESULTS AND DISUSSION

3.1 Hot-Melt Extrusion & Screw Configuration Selection

3.1.1 Thermogravimetric & DSC Analysis—Prior to HME processing, an understanding of the thermal behavior of the API and any employed excipients is critical as thermal degradation of the constituents, or an unexpected chemical reaction between the constituents, can be thermally induced. The TGA thermograms of the samples were observed for changes in weight. The thermograms indicated that the drug, excipients and

physical mixtures were chemically stable under the thermal conditions that would be employed for HME processing as only negligible weight loss near 100°C (<1%), which was attributed to adsorbed water, was observed. Thermal degradation of SC occurred at approximately 194°C. DSC data supported the findings of TGA analysis as no unexpected thermal events were observed under the same conditions. It was concluded that the temperatures necessary to process the carriers were suitable to employ. Thermal degradation of SC was observed to occur with the onset of melting at approximately 194°C (data not shown). The simultaneous melting and decomposition of SC has been previously reported and is recognized as thermally induced dissociation of Sildenafil base and citrate wherein citrate is responsible for the observed degradation.[23]

3.1.2 Polymer Screening—Binary Mixtures of the individual polymers with SC were extruded and evaluated for *in vitro* drug release in artificial salivary fluid (Figure 2). While each of the polymers that was investigated showed promising taste masking potential during preliminary screening at up to one minute, the subsequent accelerated release exhibited by Plasdone S-630 was a source of concern. A comparison the S-630 dissolution profile with 25% and 40% drug loaded ethylcellulose demonstrated a significant difference in terms of similarity factors (f_2 = 20 & 36, respectively). It was, therefore, removed from further consideration. Relative to ethylcellulose, the HPCs (grades HF, EF and ELF), too, showed a heightened, but steady release (f_2 = 45, 42 & 39, respectively, when compared to 25% drug loaded ethylcellulose). It was concluded that the initial *in vitro* drug release studies of the various carriers indicated that ethylcellulose, with 0.2% BHT as an antioxidant, provided the greatest taste masking potential and was selected for additional study. A comparison of two drug loadings (25% & 40%) in ethylcellulose was evaluated (Figure 2). At 1.5 minutes of oral dissolution the 40% drug load showed more rapid dissolution (approximately 5%). This finding was not statistically significant when the profiles were compared using the similarity factor (f_2 = 71). The lower drug loading (25% API), which was suitable for the targeted dose of SC, was selected for additional study.

3.1.3 PXRD Analysis—X-Ray diffraction was used to examine the effects of the three screw configurations on the physical state of SC in the carrier post-extrusion. Figure 3a shows the diffractogram for pure SC for comparison with the extruded formulations. The effect of the three screw configurations on the physical state of SC was considerable. The screw configuration in Figure 1a (ThermoFisher Standard Screw configuration; 40:1 L/D) resulted in highly amorphous phase SC (data not shown), which was both unnecessary and undesirable in the case of a BCS I API and was, therefore, not utilized for future processing. The amorphous form, being more readily soluble, would only serve to hinder any taste masking effects imparted by the carrier. Additionally, the amorphous form of an API is inherently less thermodynamically stable and, consequently, subject to recrystallization into various polymorphs, which have differing physical properties, if they exist.[22] This observed conversion was attributed to not only the length of the screw, and thus increased residence time in the extruder, but more significantly, the presence of three high shear mixing zones which, depending on configuration, are primarily responsible for the conversion of crystalline phases of an API to their morphologically altered, or amorphous, phases.[16]

The screw configuration in Figure 1b preserved a considerable portion of the crystalline phase of the API; however, there remained noticeable amorphicity of SC in the carrier as depicted in Figure 3b. It was speculated that the combination screw length and shear that can occur along the flight of conveying elements and the barrel of the extruder was responsible for the amorphicity noted in the diffractogram. Screw design 3 (Figure 1c) was designed to be shorter than the previous two (25:1 L/D) while still imparting sufficient distributive mixing to the melt. Indeed, despite the employment of a single mixing section in Figure 1c, in which the mixing elements were perpendicularly arranged, the diffractogram for screw configuration 3 showed enhanced preservation of the crystalline structure of SC in the carrier matrix as can be seen in the diffractogram.

3.1.4 FT-IR & Mid Infrared Chemical Imaging—Mid-infrared (MIR) spectra of crystalline and amorphous SC were collected and compared. Differences in these MIR infrared spectra allowed for differentiation between the phases in the extruded material. This was accomplished using a series of spectral derivatives to exploit the differences highlighted in the spectra (Figure 4). It has been previously reported that the unbound carbonyl, located at 1697cm^{-1} in the more organized crystalline structure, becomes shifted when it is free as is the case with Sildenafil base.[23] Additionally, virtually all of the intermolecular bonding is attributed to interaction between COOH groups in the citrate portion and the carbonyl and the amine group, which appears at 3294cm^{-1} in the crystalline form, and is shifted to 3307cm^{-1} in the amorphous form. The sulfone group, which appears at 1171cm^{-1} in the crystalline form has shifted to 1164cm^{-1} in the amorphous form. In this study, the amorphous form of SC was produced using the well-known solvent evaporation technique. The infrared images (Figures 5a-c) were produced by taking spectral derivatives of the obtained spectra and isolating spectral bands representative of the crystalline phase alone. The amorphous phase carbonyl center is shifted to 1692cm^{-1} as opposed to 1697cm^{-1} in the crystalline phase.

Figures 5a represents an infrared image of crystalline SC in the polymer matrix, post extrusion using screw configuration 2 (Figure 1b), taken at 5.5 μm spatial resolution in transmission mode with a total field of view (FOV) of 300 × 300 μm. The light blue area represents a lack of crystalline API due to either complete absence of SC or the presence of the amorphous phase. This seems to correspond well with XRD data and analysis of the same material.

Figure 5b, representative of screw configuration 3 (Figure 1c), illustrates a more uniform distribution of crystalline SC in the carrier. Here it can be seen that there exists good homogeneity of SC in the polymeric carrier as indicated by the relatively modest intensity of the carbonyl centered at 1697 cm^{-1} that this image is taken with respect to. Additionally, the pockets of crystallinity are less apparent at this spatial resolution. However, Figure 5c represents an infrared image taken with a Ge micro ATR at 1.1 μm spatial resolution with a total FOV of 70 × 70 μm. On closer inspection it is apparent that there is a slight inhomogeneity of SC in the carrier as the low intensity blue areas correspond to a complete lack of crystalline SC in that region. Additionally, the elevated yellow and regions in the images correspond to pockets of crystalline SC. These small pockets of inhomogeneity are presumably due to preserving the crystalline structure of SC. Interestingly, this

inhomogeneity showed no effect during content uniformity testing by HPLC analysis and was, therefore, considered negligible. This was presumed to be due to the small sample size used for the imaging analysis relative to the sample size utilized for HPLC analysis.

3.1.5 E-Tongue & Oral Dissolution Testing of Milled Extrudates—Electronic tongue evaluation and *in vitro* dissolution of the milled extrudates, which consisted of 20% SC loading in ethylcellulose, on the basis of screw configuration supported the physical characterization studies (FT-IR & XRD). The distance chart (Figure 6) graphically illustrates the principal component analysis results taken as a comparison of the reference or blank (artificial saliva solution). Here it is presumed that the greater the distance to the blank, the less efficient the screw configuration is for taste masking purposes. It can be seen that pure SC and the physical mixture are poorly taste masked as they exhibit the greatest distance from the blank, as would be expected. Screw configuration 1 also produced a poorly taste masked product due to the conversion of the crystalline lattice of SC to the amorphous form, which goes into solution more rapidly.

Screw configurations 2 & 3 produced comparable results on the basis of e tongue and *in vitro* oral dissolution (Figure 7); however, the results were not in complete agreement. E-tongue analysis indicated that screw configuration 3 produced a superior taste masked product, which was attributed to improved encapsulation of SC in the polymeric carrier. Additionally, FT-IR analysis indicated that the crystalline lattice was more effectively preserved when employing this configuration, which further explains the differences in e-tongue analysis. On the other hand, the dissolution data indicated screw configuration 2 produced a slightly better product in terms of taste masking.

Upon closer examination of the dissolution profiles for these screw configurations at 30 seconds, which is the maximum amount of time the formulation is expected to remain in the oral cavity, there exists a negligible difference (<1%) between the two profiles, which was further supported by the similarity factor comparison ($f_2 = 73$). These observations along with the physical characterization data, wherein it was shown that screw configuration 3 produced a more uniform crystalline dispersion, aided in deciding that screw configuration 3 would be utilized for further processing. Interestingly, there seems to exist a strong correlation between the e-tongue analysis, wherein greater distance would be indicative of greater interaction of the API with the taste sensors, and dissolution data, which indicates the amount of API in solution available for the perception of taste.

3.1.6 Addition of Release Modifying Agents—While ethylcellulose, an erodible polymer, was selected due to a very low release profile in artificial saliva, it became necessary to incorporate a release modifying agent for more rapid drug diffusion as gastric drug release was correspondingly low (data not shown). Magnesium oxide and calcium carbonate were selected as potential pore formers due to being practically insoluble near salivary pH while being completely soluble at or near gastric pH. Mannitol was also used as a pH independent pore former. Additionally, it was postulated that any dissolution of mannitol in the oral cavity could have potentially served as an additional taste masking agent as a result of being a sugar alcohol with a sweet flavor.

Initial e-tongue screening of the individual pore formers within the extruded matrices (20% each) demonstrated promising results (Figure 8) for both magnesium oxide and calcium carbonate. However, magnesium oxide produced highly erratic results during gastric dissolution screening (data not shown) and was therefore removed from consideration for further taste masking application. Based on the distance chart results for the pore formers, mannitol was also excluded from further consideration. It was observed that the quantity of mannitol needed for adequate pore forming capacity was assisting in solubilizing SC during the melt extrusion processing, which hindered the taste masking capacity of the formulations. This observation explains why mannitol ranked very closely to pure SC during the e-tongue analysis. Oral dissolution data for calcium carbonate agreed well with the e-tongue results (Figure 9) without producing the unpredictable results associated with magnesium oxide. These data were as hypothesized as calcium carbonate is insoluble near neutral pH, which should prevent the formation of diffusion promoting pores, thus keeping the exterior of the matrix intact. Because of these observations, calcium carbonate as the pore former was selected for additional studies.

3.1.7 Tableting API-Excipient Compatibility—After storage for one month under accelerated stability conditions (40°C/75% RH), HPLC analysis was conducted to evaluate the compatibility of the extruded formulations with the excipients selected for direct compression tableting (Table 3). All API-excipient compatibility samples were dried in the presence of desiccant prior to investigation in order to remove adsorbed water, which would interfere with both qualitative spectral analysis and quantitative chromatographic data analysis. API-excipient compatibility studies were evaluated qualitatively by FTIR analysis wherein the spectra were observed for the appearance and/or disappearance of previously unobserved characteristics. When no changes in the infrared spectra were observed, these samples were further evaluated quantitatively using HPLC analysis. No incompatibilities were noted.

3.1.8 Tablet Properties—Tablets containing varying levels of super disintegrant (PVP XL & XL-10) were evaluated for common tablet properties (Tables 4a & 4b respectively). The percentage of super disintegrant evaluated ranged from 2.5-10. As noted earlier, friability tends to be a common concern when formulating ODT platforms. To the contrary, these formulations exhibited excellent friability (0.8-0.32) despite having somewhat low hardness values (2.68-6.56 kp). The low hardness values are attributed to the poor compressibility and high loading (41.7%) of the milled extrudates in the ODT formulations. Interestingly, the disintegration times for the ODTs were within the acceptable limits for ODT designation (approximately 8-33 seconds depending on formulation), which are generally taken to be less than 30 seconds. While the tablets formulated with PVP XL-10 demonstrated improved hardness and friability values, those formulated with PVP XL demonstrated superior disintegration times, which is a primary concern when formulating rapidly dissolving platforms. Remarkably, tablets containing 5.0% PVP XL had average disintegration times of 8.6 seconds. With the other properties within the acceptable ranges, priority was given to disintegration time. Therefore, ODTs containing 5.0% PVP XL were selected for oral and gastric dissolution studies.

3.1.9 ODT Oral & Gastric Tablet Dissolution—Oral and gastric dissolution profiles (Figures 10) were evaluated for finished product (ODT containing 5% PVP XL) drug release. While the oral dissolution study was conducted for 60 seconds, a disintegration time of approximately 8 seconds indicates that the formulation would remain in the oral cavity for 30 seconds or less. At this time, the tablets exhibited a mere 2% drug release. The gastric release profile of the tablets indicates that excellent release can be obtained by incorporating the milled extrudates into rapidly dissolving platforms. In this case, more than 80% drug release was realized with 60 minutes.

3.1.9 Physical and Chemical Stability—The milled extrudates were assessed for physical stability of the API by both FT-IR and PXRD analysis. There was no observable difference in the spectra generated by either method indicating that that the specific polymorphic crystalline lattice had been preserved after both standard and accelerated stability testing, as would be expected. The milled extrudates were also assessed for chemical stability by HPLC analysis using the method outline in section 2.2.4, and their similarity factor ($f_2 = 89$).

4. CONCLUSION

In this study, HME was successfully employed as a processing technology for the production of taste masked formulations containing SC. This was accomplished by embedding the API in ethylcellulose along with a pH dependent pore former. The crystallinity of SC, and presumably the subsequent physical stability, was found to be dependent on the screw configuration and pore former used. FT-IR spectroscopic imaging, in tandem with conventional XRD analysis, proved to be very valuable in the evaluation of the melt-extruded formulations as it was demonstrated that preserving the crystalline structure of SC was critical for arriving at successfully taste masked formulations. The addition of calcium carbonate into the extruded formulations proved to be especially advantageous in that its pH dependent solubility helped prevent drug dissolution under oral conditions (pH 6.8) while promoting drug dissolution under gastric conditions (pH 2). The ODT formulations demonstrated uncharacteristic but excellent friability profiles without sacrificing disintegration time, which is critical for ODT formulations. E-tongue assessment of taste masking efficiency, in conjunction with dissolution data, was found to be extremely valuable and mutually supportive.

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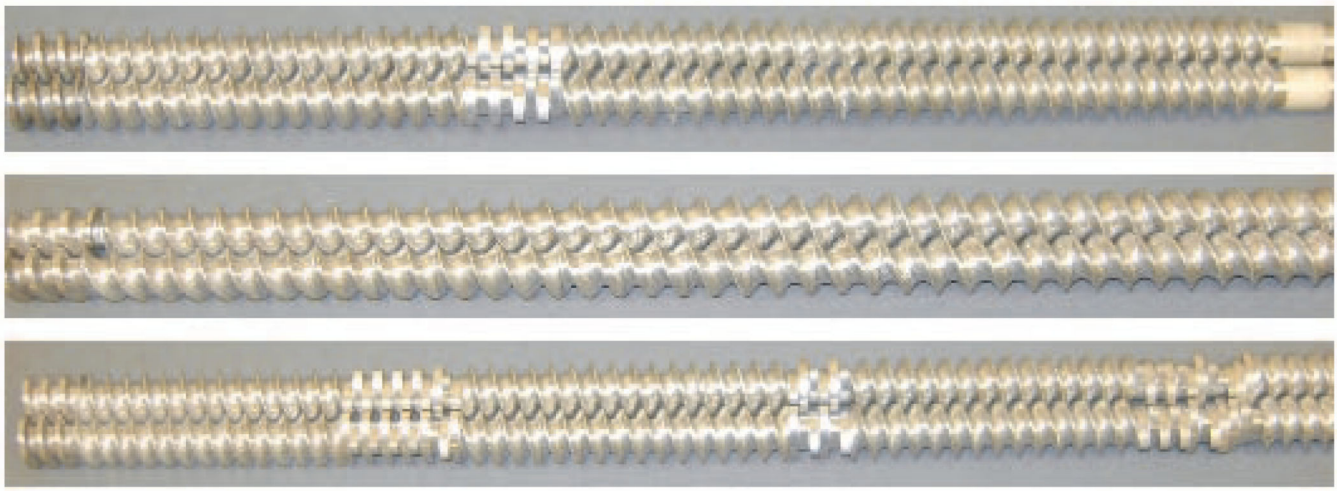


Figures 1.

1a-1c: Images of the three screw configurations evaluated during HME process optimization. Figure 1a: ThermoFisher “Standard Configuration” 40:1 L/D. Figure 2a: All conveying elements; 40:1 L/D. Figure 1c: From Left to Right: 110mm of conveying elements; 22mm of perpendicularly arranged mixing elements; 165mm of conveying elements; 25:1 L/D.

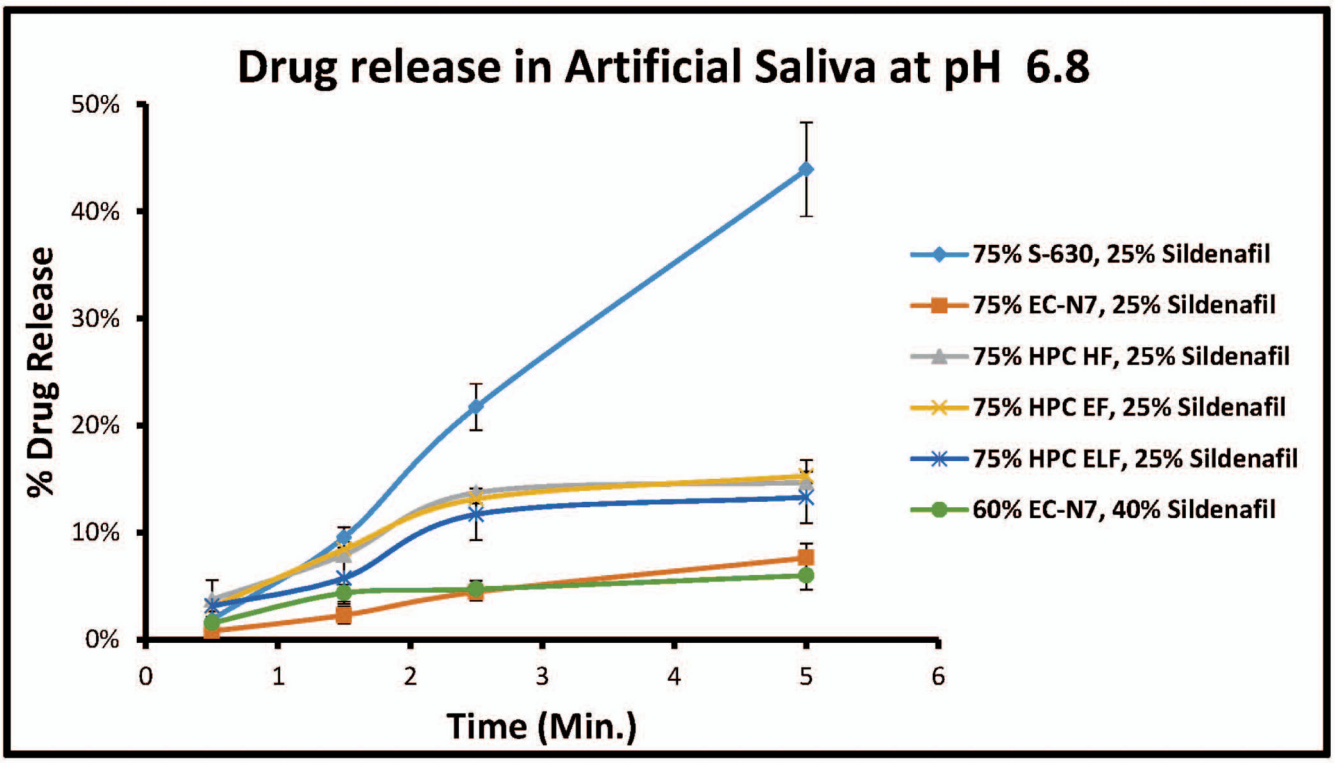
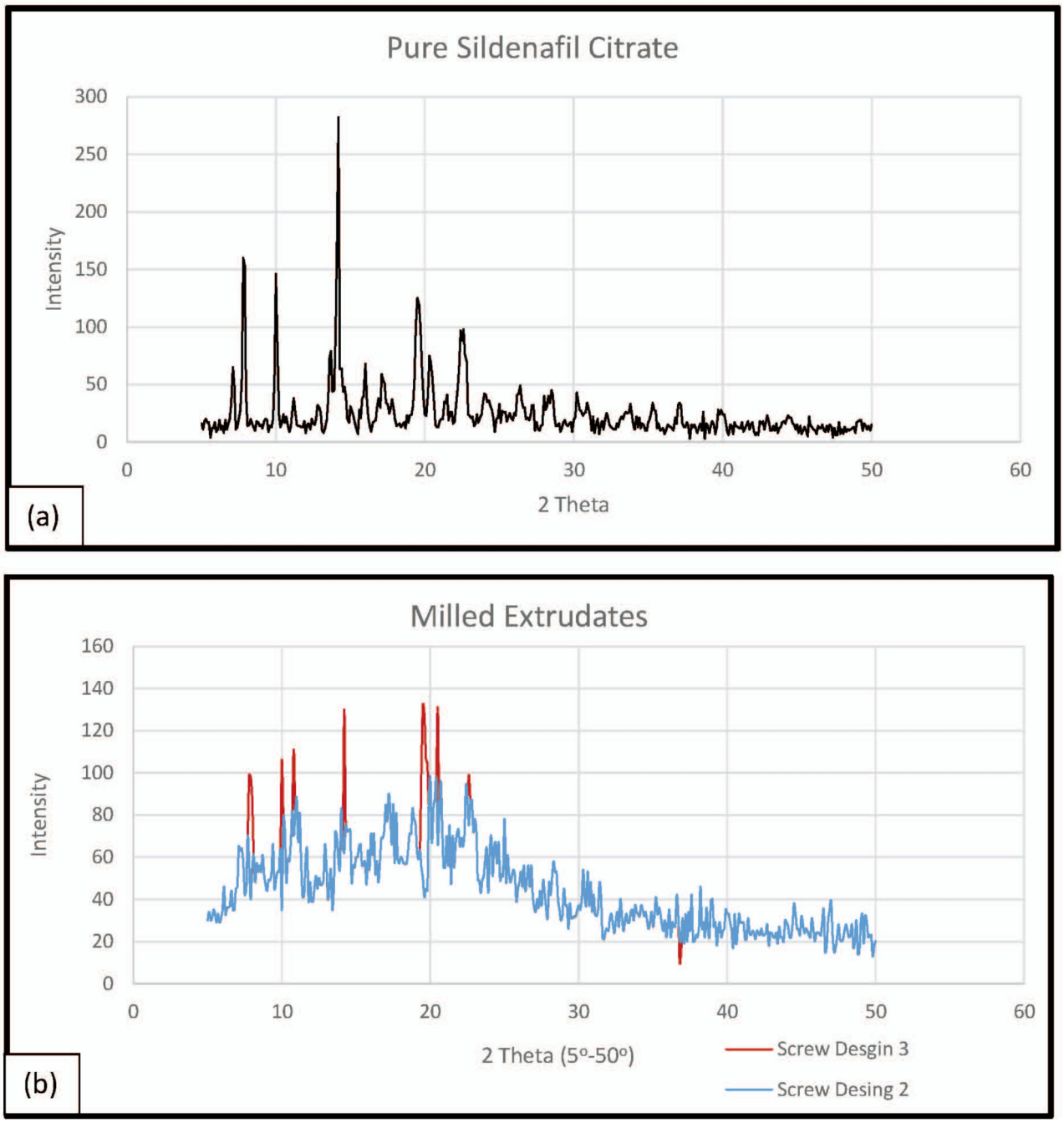


Figure 2.
SC release profile of preliminary polymer screening formulations in artificial saliva media adjusted to pH 6.8.



Figures 3.

a-b: a; PXRD diffractogram of pure crystalline SC. b; PXRD diffractograms of binary mixtures of ethylcellulose & SC as a function of screw configurations.

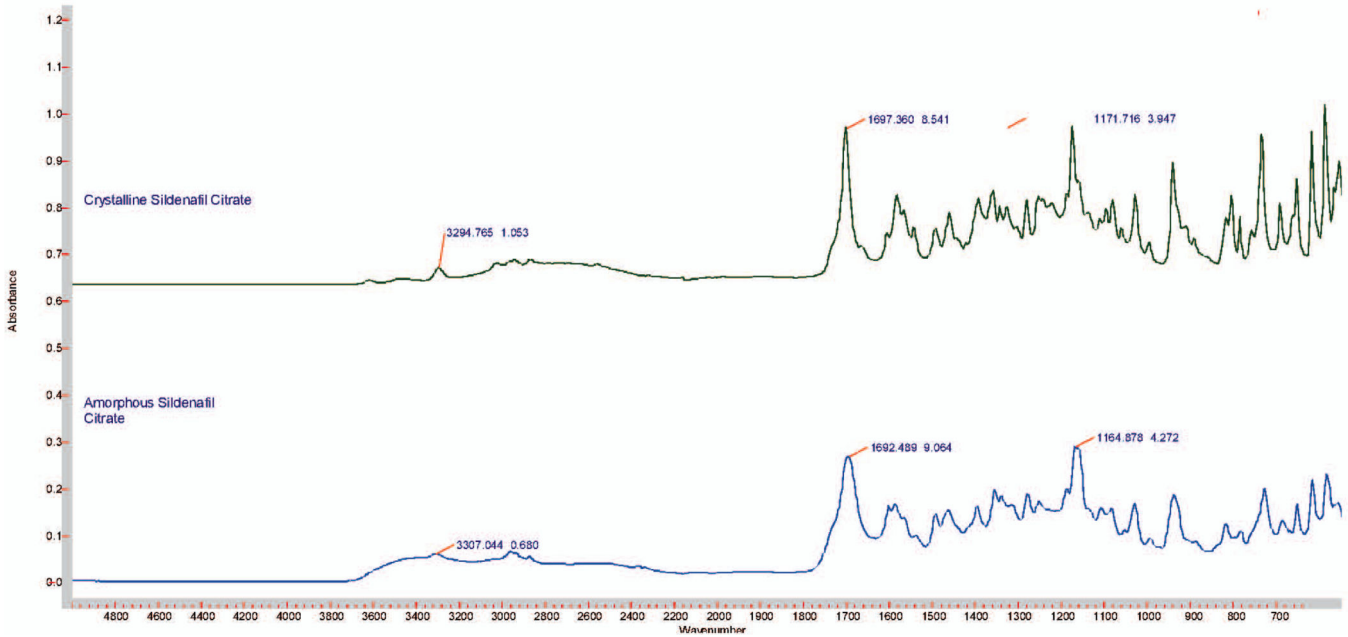


Figure 4.
FTIR spectra of crystalline and amorphous SC.

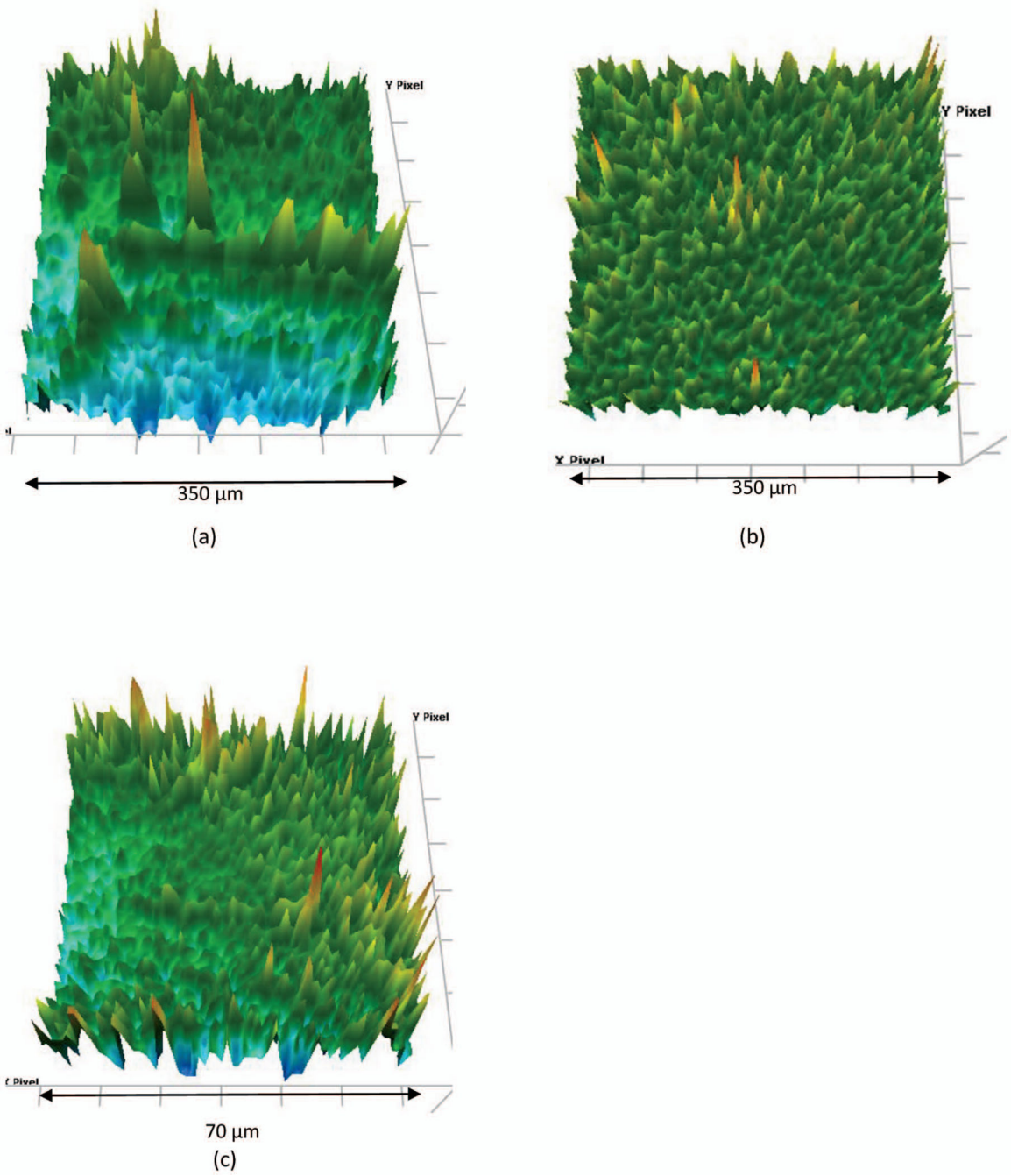


Figure 5.

a-c: Chemical image (5.5 µm spatial resolution) of a binary mixture of ethylcellulose & SC highlighting the intensity of the carbonyl present in crystalline SC processed using screw configuration 2 (Figure 1b). Figure 5b: Chemical image (5.5 µm spatial resolution) of a binary mixture of ethylcellulose & SC highlighting the intensity of the carbonyl present in crystalline SC processed using screw configuration 3 (Figure 1c). Figure 5c: Chemical image (1.1 µm spatial resolution) of a binary mixture of ethylcellulose & SC highlighting the

intensity of the carbonyl present in crystalline SC processed using screw configuration 3 (Figure 1c).

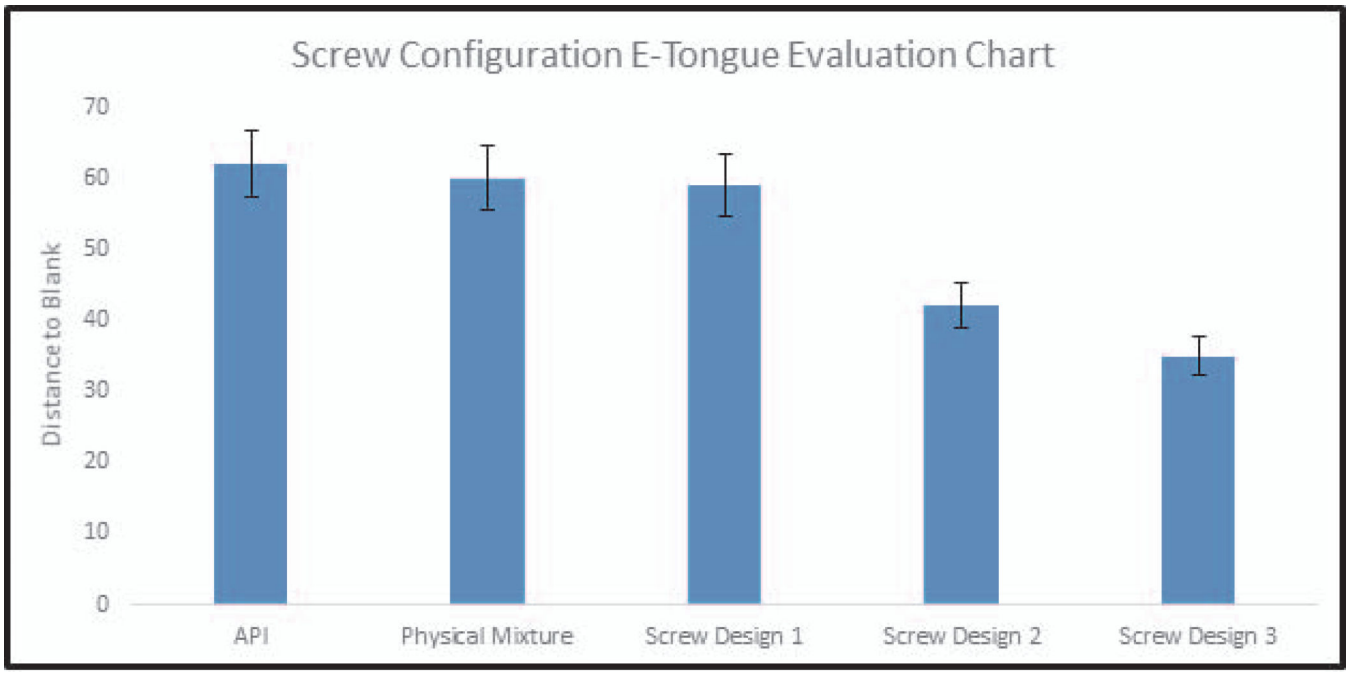


Figure 6.
Graphical illustration of PCA results from e-tongue analysis illustrating each samples distance from artificial salivary fluid as a function of screw design.

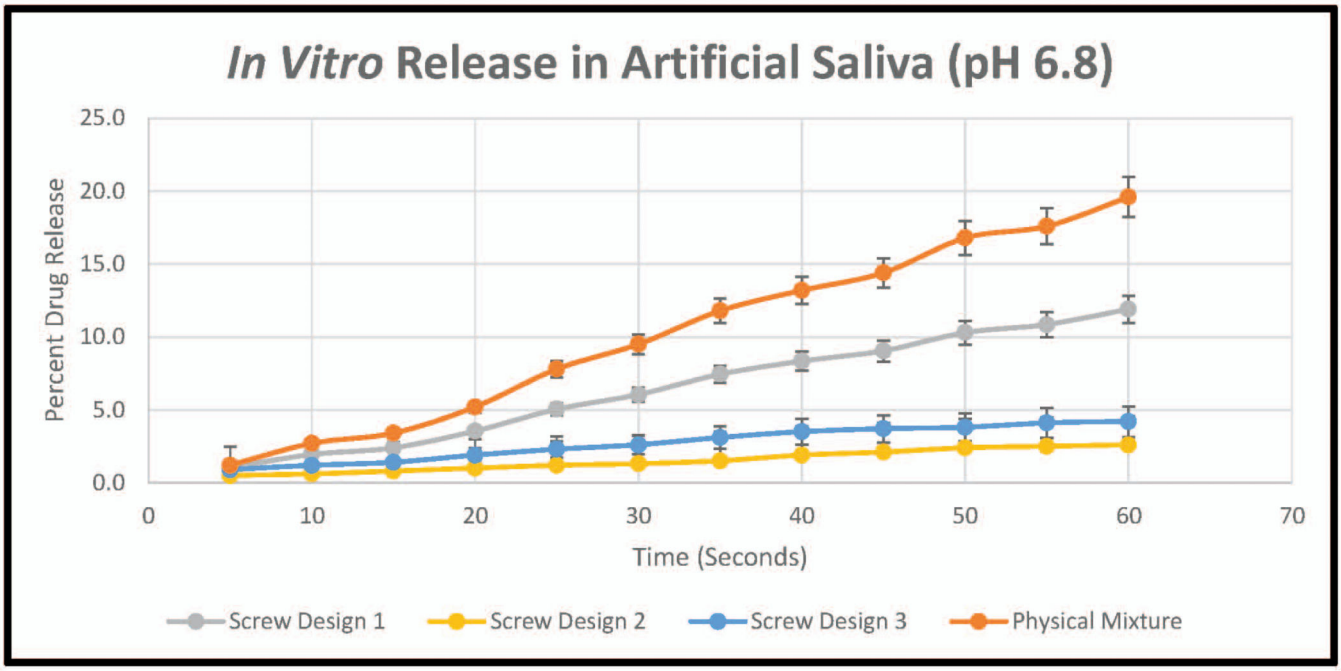


Figure 7.
Dissolution data of binary mixtures of ethylcellulose and SC as a function of screw design.

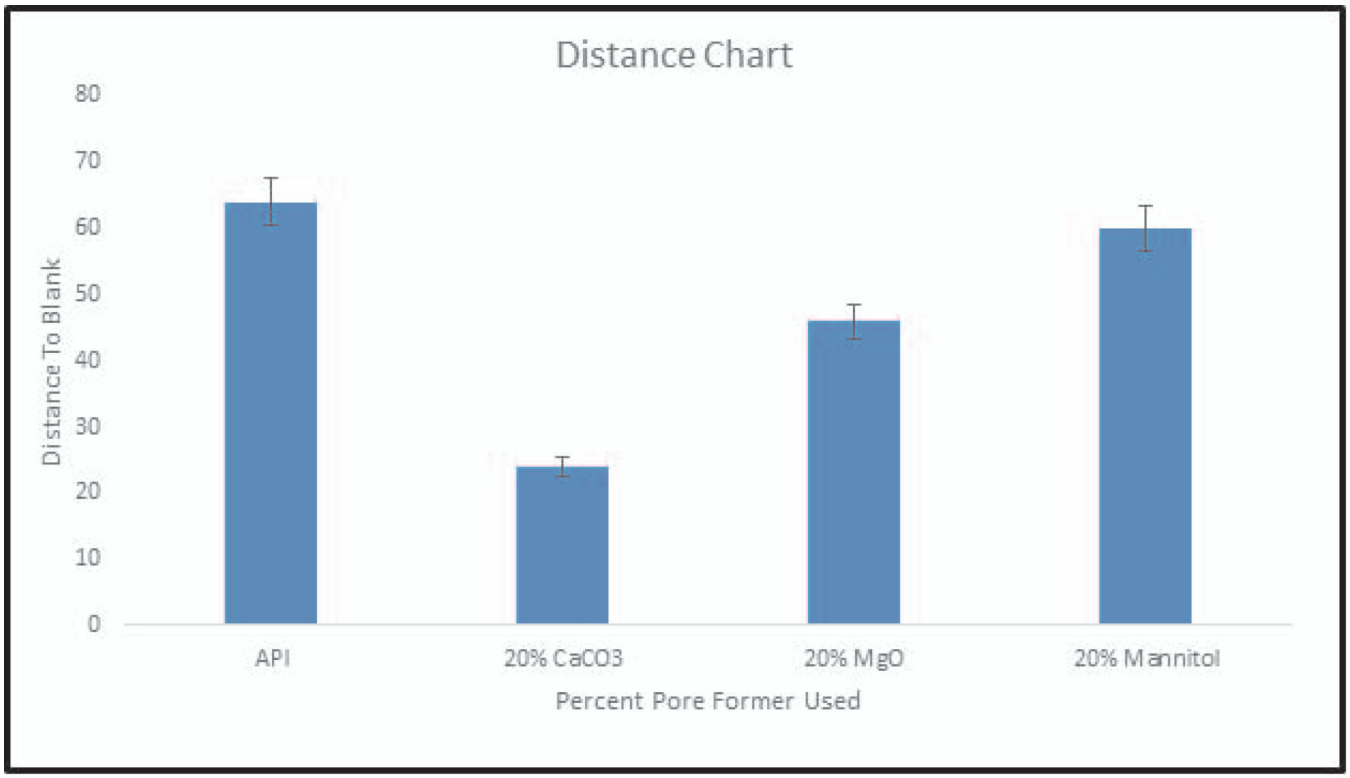


Figure 8.
Graphical illustration of PCA results from e-tongue analysis illustrating each samples distance from artificial salivary fluid as a function of individual pore former in each formulation.

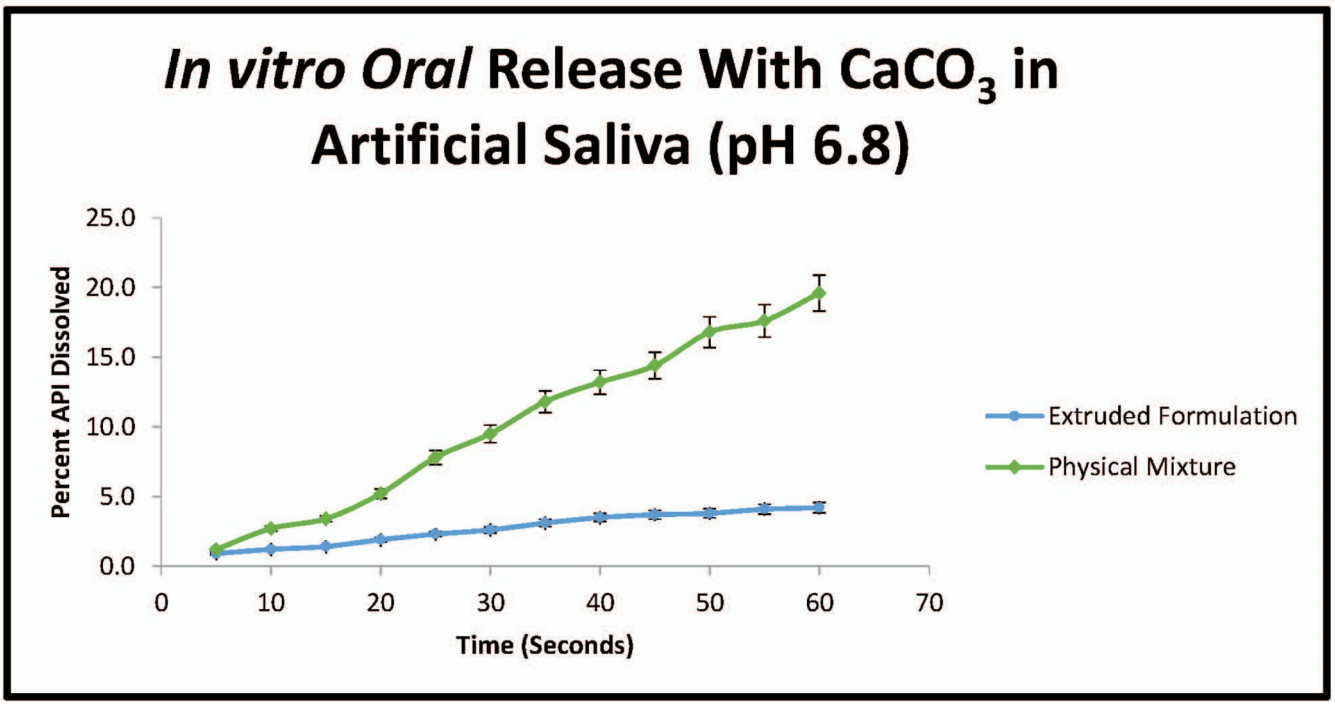


Figure 9.

Dissolution release profile of milled extrudate (20% SC, 60% ethylcellulose & 20% calcium carbonate) in artificial salivary media (pH 6.8).

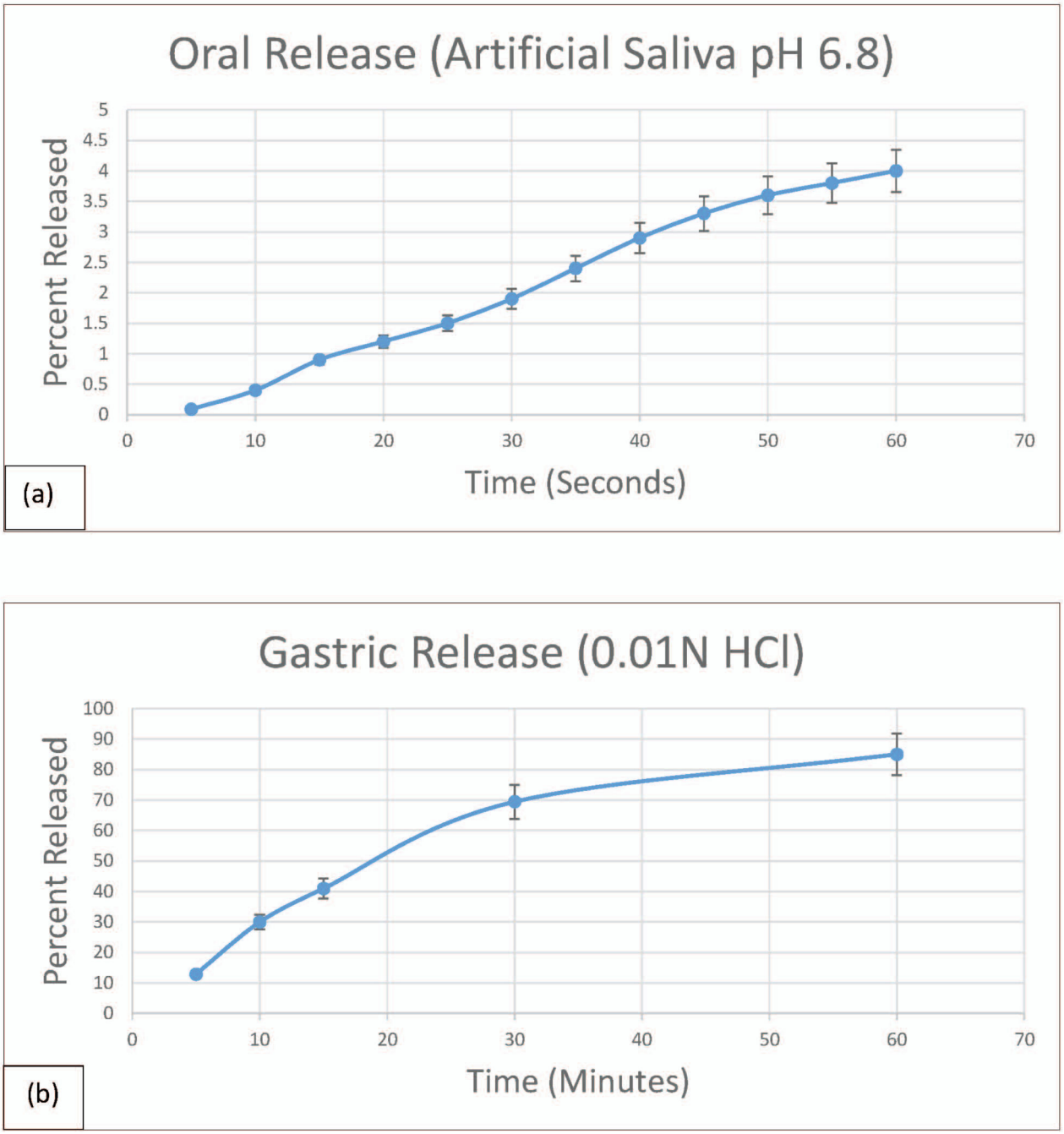


Figure 10.
Dissolution profile of optimized SC ODT formulation in artificial salivary fluid (pH 6.8)

Figure 11.
Gastric release profile of optimized SC ODT formulation in gastric media (pH 2).

Table 1

Polymer screening formulations and extrusion parameters including the final formulation

Carrier	Drug Load	Temperature Range	Screw Speed (rpm)
Plasdone® S-630 copovidone	25%	80-110°C	100
Klucel™ ELF HPC	25%	90-120°C	100
Klucel™ EF HPC	25%	90-140°C	100
Klucel™ HF HPC	25%	90-160°C	100
Aqualon™ N7 EC	25%	90-160°C	100
Aqualon™ N7 EC	40%	90-160°C	100
Aqualon™ N7 EC + $CaCO_3$ (20%)	20%	140-160°C	100

Table 2

Artificial saliva dissolution media (adjusted to pH 6.8)

Compounds	Concentration (g/L)
$CaCl_2 \cdot 2H_2O$	0.228
$MgCl_2 \cdot 6H_2O$	0.061
NaCl	1.017
$K_2CO3 \cdot 1.5H_2O$	0.603
$Na_2HPO_4 \cdot 7H_2O$	0.204
$NaH_2PO_4 \cdot H_2O$	0.273

Table 3

ODT formulation including the varying percentages of super disintegrant and filler used

Constituents	Concentration
PVP (Grades XL & XL-10)	2.5, 5 & 10%
Sucralose	1%
Magnasweet	1%
Nat. & Art. Mint Flavor	1%
Milled Extrudate	41.7% (Equivalent to 25mg of SC)
Mannitol (300DC)	52.3, 49.8 & 44.8%
Magnesium Stearate	0.5%

Table 4(a)

Tablet properties as a function of the percentage of PVP XL incorporated

	2.5% PVP XL	5.0% PVP XL	10% PVP XL
Disintegration Time (sec.)	11.3±9.1%	8.6±7.3%	9.3±17.4%
Percent Friability	0.24±2.8%	0.32±4.8%	0.19±6.6%
Thickness (mm)	4.63±1.4%	4.63±1.0%	4.67±2.2%
Hardness (kp)	3.57±17.8%	2.67±11.2%	2.89±18.9%
Loss on Drying (w/w)	2.22±20.5%	2.37±17.8%	2.66±23.7%

Table 4(b)

Tablet properties as a function of the percentage of PVP XL 10 incorporated

	2.5% PVP XL-10	5.0% PVP XL-10	10% PVP XL-10
Disintegration Time (sec.)	33.3±15.4%	27.7±9.9%	30.0±13.3%
Percent Friability	0.08±20.1%	0.23±3.4%	0.13±7.7%
Thickness (mm)	4.64±2.6%	4.63±1.9%	4.66±3.0%
Hardness (kp)	6.56±7.6%	5.68±5.4%	5.90±8.1%
Loss on Drying (w/w)	2.17±13.8%	2.34±8.7%	2.61±19.9%