

Dissolution Studies

Results of column dissolution experiments designed to evaluate the physical and chemical processes inherent to saltcake dissolution are presented along with model chemical equilibrium calculations. Two different compositions representing saltcakes in Hanford tanks were characterized, and porosities and permeabilities for a third composition based upon the saltcake waste in Tank 41H at the Savannah River Site (SRS) were also evaluated. Whereas the surrogates are all chemically similar, the presence of high phosphate loadings for the Hanford (HNF) simulants was noted as significantly affecting draining. The permeability was higher for the SRS saltcake, and the sodium nitrate loading in this saltcake was roughly 80% by weight compared to less than 60% by weight for the HNF compositions. Average values of the permeability and porosity were reduced for the surrogates based on Hanford Tanks S-112 and S-101. Here a secondary layer formed above the saltcake bed and was found to contain a large amount of gibbsite, $\text{Al}(\text{OH})_3$. Experiments with 3 molal (m) NaOH as a diluent, compared to water, did not result in additional layer formation that has been attributed to a change in local pH thereby altering the solid liquid equilibrium. Chemical analysis of the two HNF saltcakes indicated solids re-precipitation as a function of diluent added. The events were signified by large decreases in the nitrate and carbonate anion concentrations and were confined to low % dilution by weight values. Solids re-precipitation is noted as arising from the mixing of the dissolved saltcake stream with pockets of saturated interstitial liquor.

In recent years, traditional economic theory has been enriched by behavioral components. There is huge and rapidly growing evidence from empirical and experimental studies that mere profit maximization is in many cases not a good proxy of real-life decision-making and interaction in economic situations. Yet, although the concept of homo oeconomicus has subsequently been dismissed by many authors, behavior is not random or arbitrary, but follows systematic patterns and rules that researchers in the field of behavioral economics aim at understanding. This thesis adds to the understanding of actual economic decision-making by analyzing behavior in three different economic applications. The first application concerns experimental studies on the performance of partnership dissolution mechanisms. The second application studies the effects of policy instruments on a firm's incentives to invest in R&D. Finally, the third application tests the impact of responsibility for being in a disadvantageous situation through deliberate risk-taking on solidarity behavior of economic agents. Potential readership includes scholars of experimental economics in the fields of mechanism design, industrial organization and social preferences as well as interested students and practitioners involved in these areas.

Dissolution in different steps of pharmaceutical drug development was considered in this work. Dissolution is used as informative tool throughout the entire development process: After identification of a possible drug candidate, intrinsic dissolution in different buffer media is tested for physicochemical characterization. In galenics dissolution is used to develop and optimize formulations by comparative release studies. During scale-up dissolution testing is used to observe influence of process or parameter changes. For regulatory affairs all of these dissolution studies are of interest and many have to be presented to the authorities. Most of the

dissolution testing designs in pharmaceutical development are following pharmacopoeial monographs or general chapters and official guidelines. In addition these “official” dissolution testing setups, a progression of more innovative dissolution methods closer to physiological conditions are used. Devices simulating movement and flow of the GIT combined with media simulating the gastrointestinal fluids are often used. Disadvantages of these methods are that they are time-consuming and expensive, both of which limit throughput. The aims of this thesis were to (a) reduce time consumption regarding preparation of biorelevant dissolution, (b) increase biorelevance of the media FaSSIF and FeSSIF by substituting the non-physiological buffer systems for bicarbonate and (c) to increase throughput by miniaturization of dissolution devices. To meet the first goal a novel preparation method for the biorelevant media FaSSIF and FeSSIF was established. The conventional method uses chlorinated organic solvent, is time-consuming in preparation (approx. 2 hours) and needs to be done daily. The investigated method uses freeze-drying for the preparation of instant biorelevant media. The instant media only consist of bile salt and lecithin in mixed micelles. In situ preparation is done by simply adding blank buffer to the rapidly dissolving lyophilisate. Freeze-dried product gave comparable results to freshly prepared media and improved reproducibility. Comparison to commercial available instant media indicated superiority of the freeze-drying method. Next, a buffer system based on the more physiological bicarbonate buffer was investigated. A method to maintain a stable buffer system throughout the dissolution testing. The buffer therefore was created by sparging carbon dioxide into alkali saline solution to forming carbonate and bicarbonate as buffer system. At equilibrium the media was transferred to the vessels and supply of carbon dioxide continued by sparging the gas above the solution. Therewith bubble formation could be minimized, although not excluded. Only a small range of buffer strength and pH combinations was possible. The lowest pH still providing effective buffer capacity (5 mmol/l/?pH) was 5.5. Physiologically relevant buffer capacities of 10 and 30 mmol/l/?pH were tested at pH 6.5. The buffer turned out to be very sensitive against pH modifying agents by loosening its buffer capacity and strength. Standard deviations were generally higher. No superiority over conventional buffer systems like phosphate or acetate buffer regarding IVIVC was given. Therefore it is concluded that bicarbonate buffer is not a suitable medium for in vitro dissolution testing. Subsequently methods for small scale dissolution testing were established. Improvement of throughput in dissolution testing was achieved. The investigated BI miniDiss method can be used to test release profiles of small particulate formulations or intermediates. High throughput excipient screening for early formulation is possible by using the well-plate method. In the first series of tests, downscaling by factor 10 was conducted by miniaturizing and automating standard dissolution apparatus. Small vessels of 20 ml volume and paddles of about 8 mm diameter were used. Automating was done by sampling through paddle hollow shafts and online UV/VIS measurement. Since no filtration was possible due to the small sample volume, the true % dissolved was calculated using mathematical scatter correction of spectra from turbid solutions. In this way, release profiles comparable to standard dissolution testing were obtained. Cleaning and restart is accelerated and therewith throughput increased. The 10fold reduced consumption of drug formulation reduces API consumption, so that a larger variety of formulations can be prepared and tested with the same amount of API. The BI miniDiss is limited to multiparticulates like pellets,

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extrudates, minitables, granules or intermediates. Downscaling of matrix or IR tablets will likely result in different results due to changed surface to volume ratio. The well-plate method offers a miniaturization of factor 100. Dissolution of multiparticulates showed significant differences compared to standard methods. However, ranking of formulations was possible in several cases. The well-plate method is not suitable for conducting comparative release profiles. However, it can be used for selection of excipients by supersaturation testing. It is an informative tool in early formulation screening helping to optimize formulation of poorly soluble compounds. As last part of the work, the BI miniDiss was used to screen various buffers to finding the best media for IVIVC, retrospectively. The BI miniDiss proved to be useful as a fast and cost and effective screening method. In summary, several improvements in dissolution for pharmaceutical development purposes have been developed regarding consumption of API, costs and efficiency. An easy and rapid preparation of biorelevant media was established making their use in pharmaceutical development and routine quality control more feasible. The miniaturized dissolution methods and the improved high-throughput fulfil demands from pharmaceutical industries to facilitate API-saving methods in development.

Tritium removal and dissolution studies on an irradiated thoria-based fuel were conducted in the High Level Caves at the Savannah River Laboratory (SRL). The objectives of these studies were to define the effects of key process-related parameters on tritium evolution and subsequent dissolution. The test program at SRL determined the effects on tritium removal of particle size, heating temperature, oxidation, and agitation. ThO₂/UO₂ (95%/5%) fuel from the Elk River Reactor, irradiated to about 12,000 MWD/MTHM and cooled for about 12 years, was used in the tests. The thoria/uranium fuel pellets were separated from the stainless steel cladding and were divided into size fractions to determine the particle-size distribution resulting from the decladding process. In the tritium removal tests, the effect of heating several different particle-size fractions was studied at temperatures ranging from 600 to 1000°C in the presence of air for 10 to 30 hours. Each of the roasted samples (about 100 grams) was subsequently dissolved in refluxing Thorex reagent (13M HNO₃, 0.05M HF, and 0.1M Al(NO₃)₃) to determine the residual tritium. The amount of insoluble residue remaining after the dissolution was determined and characterized.

Dissolution experiments were performed on actual samples of NWCF Run H-4 radioactive calcine in fiscal years 1998 and 1999. Run H-4 is an aluminum/sodium blend calcine. Typical dissolution data indicates that between 90-95 wt% of H-4 calcine can be dissolved using 1gram of calcine per 10 mLs of 5-8M nitric acid at boiling temperature. Two liquid raffinate solutions composed of a WM-188/aluminum nitrate blend and a WM-185/aluminum nitrate blend were converted into calcine at the NWCF. Calcine made from each blend was collected and transferred to RAL for dissolution studies. The WM-188/aluminum nitrate blend calcine was dissolved with resultant solutions used as feed material for separation treatment experimentation. The WM-185/aluminum nitrate blend calcine dissolution testing was performed to determine compositional analyses of the dissolved solution and generate UDS for solid/liquid separation experiments. Analytical fusion techniques were then used to determine compositions of the solid calcine and UDS from dissolution. The results from each of these analyses were used to calculate elemental material balances around the dissolution process, validating the experimental data. This report contains all experimental data from dissolution experiments performed using both calcine blends.

As part of international agreement between the United States and Russia, a significant amount of plutonium requires disposition. One of the disposition paths is to immobilize it and dispose of it in a geological repository. The two favored immobilization forms are glass and ceramic. The plutonium, as an oxide, would be reacted with the glass or ceramic to form a homogeneous material. The resulting solid product would

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then be encased in High-Level Waste (1-ILW) glass for the can-in-canister option. The HLW glass gives a radiation barrier to increase proliferation resistance. The glass canister would then be disposed of by geological emplacement. This paper discusses how glass meets two criteria: the condition of significant actinide volatility, and That the PuO₂ feed should be incorporated into the matrix without significant amount of unreacted material.

Tablet dissolution testing where the drug release is observed as a function of time is an essential part of tablet formulation studies. These tests provide information about the dissolution mechanism and ensure the reproducibility of drug release, which is important for tablet quality assurance. However, the dissolution tests are time-consuming and thus optimal planning of experiment and sophisticated methods for its results evaluation would be needed. Identification of the parameters of specific dissolution models is crucial problem in dissolution studies. Aim of this thesis is to find the optimal time for observation of the empirical dissolution data if the parametric form of the dissolution profile is assumed to be known and the parameters should be estimated. Our approach is based on stochastic properties of the dissolution process and the Fisher information concept. Furthermore, basic models of dissolution and their stochastic modifications, including a new model based on the theory of stochastic differential equations, are presented. Parameters of studied models are estimated via maximum likelihood method. Tiivistelmä: Simuloidun polttoaineen liukeneminen graniittisessa pohjavedessä : VTT:n eluutiokokeet.

An expertly written source on the devices, systems, and technologies used in the dissolution testing of oral pharmaceutical dosage forms, this reference provides reader-friendly chapters on currently utilized equipment, equipment qualification, consideration of the gastrointestinal physiology in test design, the analysis and interpretation of data and procedure automation -laying the foundation for the creation of appropriate and useful dissolution tests according to the anticipated location and duration of drug release from the dosage form within the gastrointestinal tract.

The dissolution of Idaho Nuclear Technology and Engineering Center (INTEC) pilot plant calcines was examined to determine solubility of calcine matrix components in acidic media. Two representative pilot plant calcine types were studied: Zirconia calcine and Zirconia/ Sodium calcine. Dissolution of these calcines was evaluated using lower initial concentrations of nitric acid than used in previous tests to decrease the [H⁺] concentration in the final solutions. Lower [H⁺] concentrations contribute to more favorable TRUEX/SREX solvent extraction flowsheet performance. Dissolution and analytical results were also obtained for radioactive calcines produced using high sodium feeds blended with non-radioactive A1(NO₃)₃ solutions to dilute the sodium concentration and prevent bed agglomeration during the calcination process. Dissolution tests indicated >95 wt. % of the initial calcine mass can be dissolved using the baseline dissolution procedure, with the exception that higher initial nitric acid concentrations are required. The higher initial acid concentration is required for stoichiometric dissolution of the oxides, primarily aluminum oxide. Statistically designed experiments using pilot plant calcine were performed to determine the effect of mixing rate on dissolution efficiency. Mixing rate was determined to provide minimal effects on wt. % dissolution. The acid/calcine ratio and temperature were the predominate variables affecting the wt. % dissolution, a result consistent with previous studies using other similar types of pilot plant calcines.

Though often depicted as a rapid political transformation, the Nazi seizure of power was in fact a process that extended from the appointment of the Papen cabinet in the early summer of 1932 through the Röhm blood purge two years later. Across fourteen rigorous and carefully researched chapters, *From Weimar to Hitler* offers a compelling collective investigation of this critical period in modern German history. Each case study presents new empirical research on the crisis of Weimar democracy, the establishment of the Nazi dictatorship, and Hitler's

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consolidation of power. Together, they provide multiple perspectives on the extent to which the triumph of Nazism was historically predetermined or the product of human miscalculation and intent.

The rate-limiting step to absorption of drugs from the gastrointestinal tract is often dissolution from the dosage form. Allopurinol is a commonly used drug in the treatment of chronic gout or hyperuricaemia associated with leukaemia, radiotherapy. One of the major problems with allopurinol is that, it is practically insoluble in water, which results in poor bioavailability after oral administration. In the present study amphiphilic carrier like gelucire 50/13, PVP K30 & PEG 6000 are used in the ratio of 1:1, 1:2 and 1:4. Prepared solid dispersions were characterized in the liquid state by phase solubility studies and in the solid state by Differential Scanning calorimetric analysis, Powder X-ray diffractometry and Fourier Transform Infrared spectroscopy. The aqueous solubility of allopurinol was preferential by the presence polymer with increasing concentration. Solid state characterizations indicated that allopurinol was present as an amorphous material and entrapped in polymer matrix. Therefore, the current Research showed that gelucire 50/13 PVP K30 & PEG 6000 has a significant solubilizing effect on allopurinol.

Voloxidation is a proposed head-end process to remove tritium from irradiated LWR fuel by roasting the fuel in the presence of oxygen. The process oxidizes UO₂ to a fine U₃O₈ powder with high surface area for dissolution. Small-scale tests with irradiated Robinson, Oconee, and Saxton reactor fuels have been made to determine the dissolution behavior of both voloxidized and nonvoloxidized (UO₂) fuel. No significant technical problems were encountered in batch-dissolving of the U₃O₈ or UO₂ fuel. Dissolution rates were well-controlled in all tests. Significant observations from U₃O₈ dissolution, when compared to UO₂ dissolution, included: (1) reduced tritium and ruthenium (¹⁰⁶Ru) concentration in dissolver solutions, (2) increased weight of insoluble noble metal fission product residue (approximately 2.2X greater), and (3) increased fraction of the total plutonium which remains insoluble and is collected with the fission product residue. The insoluble plutonium was leached easily from the residue by 10M HNO₃ to ensure quantitative plutonium recovery. The weight of the fission product residue collected from both U₃O₈ and UO₂ fuels increased linearly with fuel burnup. A major fraction (> 88%) of the ⁸⁵Kr was evolved from U₃O₈ fuel during dissolution rather than voloxidation. The ⁸⁵Kr evolution rate was an appropriate monitor of fuel dissolution rate. Virtually all of the ¹²⁹I was evolved by air sparging of the dissolver solution during dissolution.

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