

REVIEW ARTICLE

Pharmaceutical Preformulation Studies – Current Review

R.Gopinath*¹, R.A.S. Naidu²¹V.L.College of Pharmacy, Raichur, Karnataka, India²MandsaurInstitute of Pharmacy, Mandsaur, M.P, India

Received 17 Jul 2011; Revised 14 Oct 2011; Accepted 21 Oct 2011

ABSTRACT

Preformulation studies carried out by various research scientists are reviewed. Preformulation begins after literature search of similar type of compounds to provide and understand (i) the degradation process, (ii) any adverse conditions relevant to the drug, (iii) bioavailability, (iv) pharmacokinetics and formulation of similar compound and (v) toxicity. Preformulation influences (a) selection of the drug candidate itself, (b) selection of formulation components, (c) API & drug product manufacturing processes, (d) determination of the most appropriate container closure system, (e) development of analytical methods, (f) assignment of API retest periods (g) the synthetic route of the API, (h) toxicological strategy. Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product quality, facilitate the implementation of new technologies, facilitate policy development and regulatory decision making. Preformulation studies give directions for development of formulation in choice of drug form, excipients, composition, physical structure, helps in adjustment of pharmacokinetic and biopharmaceutical properties, support for process development of drug substance support for PAT (Process Analytical Technology) (critical process parameters), produce necessary and useful data for development of analytical methods. According to ICH, all technical requirements for the application of drug approval were harmonized in CTD format which are scientifically more elaborate by USFDA in QOS - QbR format. QbR is based on the principle of Quality by Design (QbD) which increased efficiency in the FDA review process.

Key Words: Drug substance, Preformulation, Quality by Design (QbD), Quality Overall Summary (QOS), Question based Review (QbR)

INTRODUCTION

After drug discovery, with a background of physical, chemical and derived powered properties of the drug molecule, the drug has to be formulated in the form that can suitably be administered. The first phase of physic-chemical data collection on drug substances, evaluating potential salts thereof and excipient suitability, prior to formulation, is known as preformulation. Preformulation is the interface between new drug entity and formulation development. It also provides road map for formulation development. Preformulation involves the application of bio pharmaceutical principles to the physic chemical parameters of the drug with the goal of designing an optimum drug delivery system. Characterization of the drug molecule is the very important step at the preformulation phase of product development. Therefore, Preformulation

studies are an important tool early in the development of both API and drug products. The interaction between the drug components and the excipient used in the formulation are generally included in the study, resulting in intelligent selection of excipients. The preliminary drug degradation profiles are included in the study to guide the formulation of a stable product. A study of this subject aids the development of the monitoring process during the course of formulation development. A formal preformulation study should start at a point, after biological screening of the drug when a decision is made for further development of the compound in clinical trials. IND, NDA and ANDA guidelines issued by the US FDA and the ICH recommend preformulation studies. To develop rational, science-based requirements for drug substances and excipients which are appropriate to

a specific quality and performance objective. Preformulation investigations are designed to deliver all necessary data (especially physico-chemical, physic-mechanical and biopharmaceutical properties of drug substances, excipients and packaging materials) which may influence formulation design, method of manufacture of drug substance and drug product, pharmacokinetic / biopharmaceutical properties of the resulting product, packaging of the product. Scientific and regulatory justifications for acquiring preformulation data include the following:

1. Establishment of drug specification intended for toxicological evaluation and clinical supply preparations.
2. Formulation of clinical supplies and establishment of their preliminary specifications.
3. Providing scientific data to support dosage form development and evaluation of product efficacy, quality, stability, and bioavailability.
4. Evaluation of the stability of early developed dosage forms.
5. Fulfilment of the requirement of the CMC section of the IND and subsequent NDA / ANDA^[1].

Preformulation studies of Zidovudine derivatives were carried out by using Differential Scanning Calorimetry, Thermogravimetry, X-Ray Powder Diffractometry and Aqueous Stability Studies. X-Ray Powder Diffractometry data demonstrated that compounds 2-4 were crystalline while 5 and 6 were amorphous. DSC analysis indicated that all of them weight loss in the respective TG curves. For all compounds the aqueous hydrolysis followed a pseudo-first-order kinetics, depending on pH and the union existing between AZT and the associate moiety. The hydrolysis was catalyzed by hydroxide ion in the 7.4-13.2 pH range, while all compounds exhibited pH-independent stability from acidic to neutral media (pHs 1.0-7.4)^[2]

Preformulation and stability in biological fluids of the retrocyclin RC-101, a potential anti-HIV topical microbicide were reported. RC-101 was stable at pH 3, 4 and 7 at 25 and 37°C. High concentrations of hydrogen peroxide resulted in less than 10% reduction over 24h. RC-101 was stable in normal HVF for at least 48 h, indicating that it is a promising candidate for microbicide product development^[3].

A preformulation study and biodistribution in a rat model using liposome-encapsulated EF-24-HP β CD inclusion complex were carried out. The EF24-liposomes were evaluated for anti-proliferative activity. The results suggest that using "drug-in-CD-in liposome" approach is a

feasible strategy to formulate an effective parenteral preparation of EF24. In vitro studies show that the liposomal EF24 remains anti-proliferative, while presenting an opportunity to image its biodistribution^[4].

Preformulation evaluation of AZD1305, an oxabispidine intended for oral and intravenous treatment was carried out. The free base of AZD1305 seemed to be the most suitable agent for product development even though it has a fairly low melting point and occurred as two different crystal forms. Form B was the most stable thermodynamically in the temperature interval of interest^[5]

The impact of extractable/leachables from filters on stability of protein formulation was reported. Extractables/leachables from filter membranes may have impact on protein formulation stability and caution should be exercised during protein filtration, especially when filtering small volumes and in preformulation or high-throughput screening studies^[6].

Physico-mechanical and stability evaluation of carbamazepine cocrystal with nicotinamide was carried out. The cocrystals were fluffy, with a needle-shaped crystal, and low intrinsic dissolution rate. The solubility profiles of the cocrystals were similar to CBZ, but its intrinsic dissolution rate was lower. Unlike CBZ, the cocrystals were resistant to hydrate transformation and plastic deformation started at a higher compression pressure in the cocrystals than CBZ, as indicated by the high yield pressure^[7].

Solubilisation of the novel anionic amphiphilic photosensitizer TPCS 2a by nonionic Pluronic block copolymers was performed. The Pluronic block copolymers solubilized the photosensitizer above CMC at ambient temperature^[8].

Poly (lactide-co-glycolide) nanoparticles (NP) containing Doxorubicin (DOX) along with a nitric oxide (NO) donor Sodium Nitroprusside (SNP) were prepared by solvent displacement. NO is expected to synergise with antileishmanial activity of DOX. Preformulation studies showed no significant interaction between Doxorubicin (DOX) and Sodium Nitroprusside^[9].

The applicability of the semi-fluorinated alkane 1-perfluorohexyloctane (F6H8) as a novel excipient in lipid based drug delivery systems was studied. Solubility studies of 11 poorly water soluble drugs (cinnarizine, danazol, estradiol, fenofibrate, griseofulvin, halofantrine, lidocaine, prednisolone, probucol, rolipram and siramesine) showed significantly lower equilibrium solubility in F6H8 compared to soy bean oil (long chain

triglyceride). The applicability of F6H8 as an excipient for future use in lipid based formulations for poorly water soluble drugs is therefore considered to be very limited^[10].

Characterization of nicergoline polymorphs crystallized in several organic solvents was done. Nicergoline (NIC), a poorly water-soluble semisynthetic ergot derivative, was crystallized from several organic solvents, obtaining two different polymorphic forms, the triclinic form I and the orthorhombic form II. Preformulation studies might encourage industry for the evaluation of polymorph II, as it is more suitable for pharmaceutical applications^[11].

NPC 1161C is a novel antimalarial drug and the mean pK(a1), pK(a2), and pK(a3) were determined to be 10.12, 4.07, and 1.88, respectively. The aqueous solubility was found to be 2.4×10^{-4} M having a saturated solution pH of 4.3–5.0 and a low intrinsic solubility of 1.6×10^{-6} M. An exponential decrease in solubility was observed with increasing pH. Meanlog P of the salt and the free base were estimated to be 2.18 and 3.70, respectively. The compound had poor stability at pH 7.0 at 37 °C, with a t (90) of 3.58 days. Thermal analysis of the drug using DSC and TGA revealed that the drug is present as a semi-crystalline powder, which transformed into the amorphous state after melting^[12].

Due to nifedipine's poor water solubility and erratic bioavailability, complexation with selected cyclodextrins was studied in order to overcome these limitations. The aim was to develop a quantitative structure property relationship (QSPR) to identify cyclodextrin molecular properties important in complex formation and provide a predictive tool which would be valuable during preformulation studies. The QSPR developed indicates that the major driving forces for nifedipine complexation, in addition to cyclodextrin concentration, are hydrophobicity and Van der Waals interactions (3D solubility parameters, hydrophilic surface area and differential connectivity index)^[13].

A preformulation study of a new medicine for Chagas disease treatment: physicochemical characterization, thermal stability, and compatibility of benznidazole. The compatibility study was conducted by binary mixtures (1:1, w/w) of the drug with microcrystalline cellulose 102 and 250, anhydrous lactose, and sodium starch glycolate. The compatibility study evidenced two possible chemical incompatibilities between BNZ and the tested excipients. The BNZ reaction with anhydrous lactose is more

pronounced than with the sodium starch glycolate because the lactose has more free hydroxyl groups to undergo reduction by the drug stability^[14].

Risk assessment and physicochemical characterization of a metastable dehydrate API phase for intravenous formulation development was carried out. (1S,5R)-2-[[[(4S)-azepan-4-ylamino]carbonyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (Compound 1) is a β -lactamase inhibitor for intravenous administration can exist as an amorphous solid and four distinct crystalline phases A, B, C, and D in the state. In aqueous formulations, the dihydrate form of the API was predominant and, due to the more favorable solubility and dissolution profile required for preclinical and clinical studies, a metastable form of the API was selected, and the risks associated with developing this form were evaluated^[15].

Although efficient in vitro, fenretinide has not been successful clinically for either of the targeted indications—cancer prevention and dry age-related macular degeneration—because of various issues, such as low oral bioavailability. Therefore, controlled release carriers for parenteral delivery of fenretinide were developed. Injectable carriers for fenretinide were successfully prepared, exhibiting excellent drug stability. Based on the *In vitro* release properties of the different carriers, the preferred injection sites and in vivo release rates will be determined in future preclinical studies^[16].

Hot melt extrusion (HME) and KinetiSol Dispersing (KSD) were utilized to prepare dissolution-enhanced solid dispersions of Roche Research Compound A (ROA), a BCS class II drug. Preformulation characterization studies showed that ROA was chemically unstable at elevated temperatures and acidic pH values. Eudragit L100-55 and ACOAT LF (HPMCAS) were evaluated as carrier polymers. Compositions containing HPMCAS were also prepared by HME, but an amorphous dispersion could not be obtained. All HME compositions contained ROA-related impurities. KSD was investigated as a method to reduce the decomposition of ROA while rendering compositions amorphous. The results of the study demonstrated that KSD is an effective method of forming dissolution-enhanced amorphous solid solutions in cases where HME is not a feasible technique^[17].

Resveratrol and resveratrol glucoside (piceid) were evaluated in a preformulation stability study. An HPLC assay was used for the analysis of stressed/reference samples. Samples of solid,

crystalline material were held under the following conditions: 40 degrees C/75% RH (both open and protected), ambient fluorescent light (open), 70 degrees C (open), and exposed using a light cabinet to achieve ICH conditions for UV/fluorescent light. Both compounds were found to be stable out to 3 months for both accelerated and ambient conditions with negligible degradation. Exposure to UV and fluorescent light under ICH conditions did not significantly degrade the solid materials for UV exposure at 3 times the ICH limit and for fluorescent light exposure at 1 times the ICH limit. The results presented demonstrate crystalline resveratrol and piceid are stable solids. No evidence of oxidation of either material by atmospheric oxidants was seen. The data reported may help to clarify widely held beliefs that resveratrol is unstable and extremely sensitive to oxidation/degradation^[18].

Physicochemical properties of drug molecules impact many aspects of both in and in vitro behaviour. Poor physicochemical properties can often create a significant impediment to establishing reliable SAR, establishing proof of principle type studies using in vivo models, and eventually leading to added performance variability and costs throughout the development life cycle; in the worst case scenario, even preventing execution of the desired development plan. This review will discuss the key physicochemical properties and how they can be assessed and how they are implicated in both discovery enablement and in final product developability of the selected candidate^[19].

In protein formulation development, shaking stress is often employed to assess the physical stability of antibody formulations against aggregation. Since there are currently no guidelines describing suitable test conditions, very different shaking stress designs are used. These different designs may influence the resulting stability data. Small scale shaking stress experiments were performed with different monoclonal IgG antibodies (as buffered solutions or marketed formulations). This experimental setup led to clearly different stability results for buffered solutions and marketed products. Moreover, this setup required only relatively small amounts of protein solution which is advantageous in preformulation studies^[20].

Many techniques for the production of solid dispersions rely on elevated temperatures and prolonged material residence times, which can

result in decomposition of temperature-sensitive components. In this study, hydrocortisone was used as a model temperature-sensitive active ingredient to study the effect of formulation and processing techniques as well as to characterize the benefits of KinetiSol Dispersing for the production of solid dispersions. Preformulation studies showed that vinyl acetate:vinylpyrrolidone (PVPVA) copolymer allowed for hydrocortisone dissolution within the carrier at temperatures as low as 160 degrees C, while hydroxypropyl methylcellulose required temperatures upward of 180 degrees C to facilitate solubilisation. Low substituted hydroxypropyl cellulose, a high glass transition temperature control, showed that the material was unable to solubilise hydrocortisone. Manufacturing process control studies using hot melt extruded compositions of hydrocortisone and PVPVA showed that increased temperatures and residence times negatively impacted product potency due to decomposition. Using KinetiSol Dispersing to reduce residence time and to facilitate lower temperature processing, it was possible to produce solid dispersions with improved product potency. KinetiSol Dispersing provided significant advantages over hot melt extrusion due to the reduced residence times and lower required processing temperatures. This allowed for the production of solid dispersions with enhanced product potency^[21].

Apomine is a novel compound that inhibits the mevalonate/isoprenoid pathway of cholesterol synthesis and may prove effective as a skin cancer chemoprevention therapy. Preformulation included the influence of pH, buffer species, ionic strength, and organic solvents on the stability of apomine at four different temperatures. Apomine was determined to undergo apparent first-order degradation kinetics for all conditions evaluated. Apomine undergoes base-catalyzed degradation. Less than 15% degradation is observed after >200 days under acidic conditions. Long-term stability studies were performed on two different topical cream formulations and indicate that both formulations are chemically stable for over 1 year at both 4 and 23 degrees C. The efficacy of topically applied apomine, from ethanol and developed 1% cream, was evaluated in vivo against the incidence of melanoma. Regardless of delivery vehicle apomine treatment caused a significant reduction in tumour incidence.^[22]

The new SeDeM Diagram expert system was used to analyze the suitability of 43 excipients for direct compression with disintegrant properties from

eight chemical families. This study, which was based on the current concept of "Quality by Design ICH Q8", evaluated the pharmacotechnical properties of disintegrants in powder form and selected the candidates that were most suitable for direct compression and their use in formulation of orally disintegrating tablets (ODT). It was concluded that nine disintegrants had an SeDeM value with the index of good compression (IGC) over 5. Most of these disintegrants were from the microcellulose family. Other disintegrants had indexes that were close to 5. It is assumed that these excipients can be used in direct compression, when they are added to other excipients^[23].

Following the production of spray-dried mannitol powders, it is essential that the polymorphic content of each individual product is completely characterized. The implications of the polymorphic behaviour of mannitol are immense. The appearance or disappearance of a crystalline form within a dosage form can have costly repercussions and lead to a dosage form being withdrawn. In this study, commercially available and laboratory-produced spray-dried mannitol products were characterized to establish the polymorphic content of each. Structural analysis revealed that alpha- and beta- polymorphic forms were present in the commercial samples and some contained a mixture of polymorphs. Reprocessing employing spray drying indicated alpha- to beta-polymorphic transitions occurred within some of the samples. It is essential that preformulation studies where spray-dried mannitol products are to be employed must take into account its polymorphic behaviour upon supply, processing, and subsequent storage^[24].

Therapeutic proteins are exposed to various wetted surfaces that could shed subvisible particles. In this work we measured the adsorption of a monoclonal antibody (mAb) to various microparticles, characterized the adsorbed mAb secondary structure, and determined the reversibility of adsorption. During incubation studies, exposure to the air-water interface was a significant cause of aggregation but acted independently of the effects of microparticles. Incubations with glass, cellulose, stainless steel, or Fe(2)O(3) microparticles gave very different results. Cellulose preferentially adsorbed aggregates from solution. Glass and Fe(2)O(3) adsorbed the mAb but did not cause aggregation. Adsorption to stainless steel microparticles was irreversible, and caused appearance of soluble aggregates upon incubation. The secondary

structure of mAb adsorbed to glass and cellulose was near-native^[25].

The solubility and dissolution rate of active ingredients are of major importance in preformulation studies of pharmaceutical dosage forms. In the present study, passively absorbed drugs are classified based on their intrinsic dissolution rate (IDR) and their intestinal permeabilities. IDR was determined by measuring the dissolution of a non-disintegrating disk of drug, and effective intestinal permeability of tested drugs in rat jejunum was determined using single perfusion technique. According to the results obtained and proposed classification of drugs, it is concluded that drugs could be categorized correctly based on their IDR and intestinal permeability values^[26].

The aim of the present work was to improve the solubility and dissolution profile of irbesartan (IRB), a poorly water-soluble drug by formation of inclusion complex with beta-cyclodextrin (betaCD). The stability constant (K(s)) was found to be 104.39 M(-1). IRB-betaCD binary systems were prepared by cogrinding, kneading using alcohol, kneading using aqueous alcohol, and coevaporation methods. Among the various methods, coevaporation was the best in which the solubility was increased and dissolution rate of the drug was the highest. The study indicated the usefulness of cyclodextrin technology to overcome the solubility problem of IRB^[27].

Development of optimal formulation conditions stabilizing live attenuated bacterial vaccines is impeded by traditional methods used for viability measurement. To facilitate preformulation studies of such vaccines, spectroscopic techniques capable of providing real-time and high throughput information have been employed to obtain a global stability profile for a live attenuated Ty21a bacterial typhoid vaccine over a wide range of pH (4 to 8) and temperature (10 to 85 degrees C). Using the data obtained from fluorescence and circular dichroism techniques, an empirical phase diagram (EPD) has been subsequently constructed, which suggests that Ty21a cells exist in at least four apparent physical phases related to different viability states, with the most stable phase at pH 6 and 7 at temperatures below 30 degrees C. A slightly basic pH (pH 8) appears to decrease the fluidity of the cell membrane, whereas acidic pH conditions are detrimental to membrane integrity over the entire temperature range amongst other promising stabilizers, 10% sucrose and 0.15 M glutamic acid display the greatest protective effects, with an

increase of about 10 degrees C in the transition temperature of Ty21a cells^[28].

A pH-dependent sustained release tablet formulation of a poorly water soluble and acid labile tegaserod maleate (TM) was developed using a combination of Eudragit L100 and Eudragit S100 and to allow the dosage form to pass through the stomach intact, start disintegrating in the upper small intestine and slowly release the active in a controlled manner. Partition coefficient, contact angle and drug-excipient compatibility were investigated as part of the preformulation studies. The effects of solubilizer, disintegrant, binder, coating polymer concentration, pore former, and plasticizer on the drug release rate were determined. The results demonstrated that approximately 90% of the drug was released in a sustained release manner in the pH 6.8 phosphate buffer within 12 h while no drug was detected when subjected to drug release studies in 0.1 mol/L hydrochloric acid for 2 h^[29].

The preformulation of insoluble drugs, trimethoprim and nitrofurantoin, was studied in order to achieve a suspension with desirable requirements. The objective of the formulator is to avoid the irreversible aggregation called "caking", and to obtain a suspension with airy, large volume sediment easily redispersible and with suitable rheological properties. An experimental design useful to determine optimal properties is a Box-Behnken design. The surfactant, thickener and electrolyte at different proportions were the three factors studied. This strategy allows to point on the main significant effect and to determine the concentrations of each product leading to optimal properties of the suspensions^[30].

The investigation was carried out to study the influence of different types of chitosan and of the preparation technique of the drug-polymer combination in improving the dissolution and permeation abilities of naproxen, a very poorly water-soluble anti-inflammatory drug. Drug-chitosan systems were prepared by simple physical mixing, kneading, cogrinding, or coevaporation using five types of chitosan (base and glutamate or hydrochloride salts, both at two different molecular weights). The products were tested for drug-dissolution behaviour and for permeation properties through both Caco-2 cell mono layers and artificial lipophilic membranes. All combinations with chitosan base were significantly ($p < .01$) more effective in enhancing drug-dissolution rate than those with both its salts, probably in virtue of its higher amorphizing effect

toward the drug, as observed in solid-state studies. Cogrinding was the most powerful technique in promoting both dissolution and permeation properties of the drug, thus pointing out the importance of the preparation method in obtaining efficacious drug-carrier systems. The good correspondence between permeation experiments with Caco-2 cells and those with the artificial lipophilic membrane indicated the suitability of this latter in preformulation studies for a rapid screening of the best carrier and the most efficient drug-carrier preparation method for improving the pharmaceutical properties of drugs^[31].

Preformulation studies were performed on a hemiglutarate ester prodrug of Delta(9)-tetrahydrocannabinol (THC-HG), to facilitate the development of stable formulations by hot-melt methods. The prodrug exhibited a seven-fold higher aqueous solubility as compared to the parent drug (THC). Also, the solubility of the compound increased with increasing pH, being maximum at pH8. The prodrug exhibited a v-shaped pH-rate profile, with the degradation rate minimum between pH 3 and 4. The moisture uptake and drug degradation increased with an increase in relative humidity. Solid-state stability indicated that the prodrug was stable at -18 degrees C but demonstrated higher degradation at 4 degrees C, 25 degrees C and 40 degrees C (51.6%, 74.5% and 90.1%, respectively) at the end of 3-months. THC-HG was found to be sensitive to the presence of oxygen^[32].

Docetaxel, a widely used anticancer agent, has sparingly low aqueous solubility. Tween 80 and ethanol need to be added into its formulation, probably resulting in the toxic effects.

It was aimed to prepare submicron lipid emulsions as a carrier of docetaxel to avoid these potential toxic vehicles. Preformulation study was performed for rational emulsions formulation design, including drug solubility, distribution between oil and water, and degradation kinetics. The optimal formulation of docetaxel is composed of 10% oil phase, 1.2% soybean lecithin, 0.3% Pluronic F68, and 0.4 or 0.8 mg/mL docetaxel, with particle size in the nanometre range, entrapment efficiency more than 90%, and is physicochemically stable at 4 and 25 degrees C for 6 months. Animal studies showed that docetaxel emulsion has significantly higher area under the curve (AUC) and C(max) in rats compared to its micellar solution. The results suggested that the submicron lipids emulsion is a promising intravenous carrier for docetaxel in place of its present commercially available

docetaxel micellar solution with potential toxic effects^[33].

The current study was carried out to investigate the ability of citric acid monohydrate (CA MH) to enhance the release of diltiazem hydrochloride from melt extruded Eudragit RS

PO tablets and to eliminate drug particle size effects. The drug release from systems with constant drug-to-polymer ratio was significantly increased when CA MH was added as a result of enhanced poreformation. Particle size effects were eliminated when large amounts of CA MH were used due to the loss of drug crystallinity. Matrix tablets with CA MH furthermore showed a faster and more complete drug release compared to systems with drug only or alternative pore formers (sucrose, NaCl, or PEG 3350). CA MH promoted the miscibility between the drug and Eudragit RS PO during hot-melt extrusion, resulting in the extrusion of an amorphous system with improved dissolution characteristics^[34].

Once daily sustained release tablet of aceclofenac using chitosan and an enteric coating polymer (hydroxypropylmethylcellulose phthalate or cellulose acetate phthalate) was developed. Overall sustained release for 24 h was achieved by preparing a double-layer tablet in which the immediate release layer was formulated for a prompt release of the drug and the sustained release layer was designed to achieve a prolonged release of drug. The preformulation studies like IR spectroscopic and differential scanning calorimetry showed the absence of drug-excipient interactions. The optimized tablets were stable at accelerated storage conditions for 6 months with respect to drug content and physical appearance^[35].

Practical examples of preformulation support of the form selected for formulation development are provided using several drug substances (DSs). The examples include determination of the solubilities vs. pH. The results from two model excipient compatibility methods are compared to determine which has better predictive accuracy for room temperature stability. A DSC (calorimetric) method and an isothermal stress with quantitative analysis (ISQA) method that simulates wet granulation conditions were compared using a 2 year room temperature sample set as reference. An example of a pH stability profile for understanding stability and extrapolating stability to other environments is provided. Dissolution method requirements for CR dosage forms are discussed. The applicability of a modified disintegration time (DT) apparatus for supporting

CR dosage form development of a pH sensitive DS at a specific pH such as duodenal pH 5.6 is related. This method is applicable for DSs such as peptides, proteins, enzymes and natural products where physical observation can be used in place of a difficult to perform analytical method, saving resources and providing rapid preformulation support^[36].

The preformulation, solubilisation and pharmacokinetic evaluation of antalarmin, a stress inhibitor, have been conducted. Antalarmin has a poor water solubility of less than 1 microg/mL and is weakly basic with an experimentally determined pK(a) of 5.0. Three of these formulations are aqueous solutions (10% ethanol + 40% propylene glycol; 20% cremophor EL; 20% sulfobutylether-beta-cyclodextrin) each buffered at pH 1. The fourth formulation is a lipid-based formulation comprising of 20% oleic acid, 40% cremophor EL and 40% Labrasol. Only the lipid-based formulation successfully resisted drug precipitation following dilution with enzyme free simulated intestinal fluid. The lipid-based formulation resulted in over 12-fold higher bioavailability as compared to the suspension formulation, the highest amongst the formulations examined^[37].

The objective of this study was to prepare and evaluate in vitro the bioadhesive gels of 5-Fluorouracil (FU) for the treatment of oropharyngeal cancer. In preformulation study, the physicochemical interactions between FU and polymers were investigated. According to FTIR, XRD, and DSC studies, the drug did not show any evidence of an interaction with the polymers used and was present in an unchanged state. The gel formulations containing FU were prepared by using Poloxamer 407, HPMC K 15 M, and Gantrez S-97 (polymethylvinylether-co-maleic anhydride). The bioadhesiveness of the gels was found to increase with increasing proportion of HPMC K 15 M and Gantrez S-97. The permeability coefficients (Kp) of gel across cellulose membrane and buccal mucosal membrane were differed significantly ($p < 0.05$). The pH of the release medium showed a very slight effect on the release of FU^[38].

N-Epoxyethyl-1, 8-naphthalimide (ENA) is a novel antiproliferative drug candidate with potent anticancer and antifungal activity. It has an aqueous solubility of 0.0116 mg/mL and also exhibits hydrolytic instability with a first-order hydrolysis rate of 0.051 h⁻¹. ENA solubilization was investigated in both aqueous media and nonaqueous solutions. It is found that none of the

solubilization techniques in aqueous media could increase ENA solubility to a desired level of several hundred microg/mL at pharmaceutically acceptable excipient concentrations (< or =10%). In contrast, a combination of 70% Cremophor EL and 30% ethanol (v/v) proved effective in solubilizing ENA at 4 mg/mL, which exhibited good physical and chemical stability on storage at both 4 degrees C and room temperature over 4 months. No precipitation was observed upon 5-20 times dilution by the saline; in addition, less than 5% of ENA was hydrolysed in 4h for the saline-diluted aqueous solutions. The approach used in this work could serve as a useful reference in formulating nonpolar drugs with hydrolytic instability^[39].

To enhance the physical stability of *Clostridium difficile* toxoids A and B, screening for stabilizing compounds was performed. The screening of 30 GRAS compounds at various concentrations and in several combinations was performed^[40].

The objective of the work was to assess the possible interactions between the model drug diclofenac sodium (DS) and the water-insoluble ammonio methacrylate copolymer (AMC). Films with different drug/polymer ratios were therefore prepared by the solvent casting method and investigated as a preformulation study towards sustained release microparticles. Thermoanalytical studies confirmed that the DS could behave as a plasticizer, which was indicated by decreasing glass transition temperature (*T_g*) of the AMC, depending on its dispersity level in the AMC matrix. Partially solid solutions were formed at DS/AMC ratios of 1:12, 1:8 and 1:6. The DS was mainly crystalline at DS/AMC ratio of 1:4, while it remained crystalline at a ratio of 1:2^[41].

To formulate compounds sparingly soluble in water, pharmaceutically acceptable cosolvents or surfactants are typically employed to increase solubility. Compounds poorly soluble also in these systems will likely show severe formulation issues. In such cases, relatively high amount of compounds, rarely available in the early preclinical phases, are needed to identify the most appropriate dosing vehicles. Hence, the purpose of this study was to build two computational models which, on the basis of the molecular structure, are able to predict the compound solubility in two vehicle systems (40% PEG400/water and 10% Tween80/water) used as screening tools for anticipating potential formulation issues. Since only a small number of 2D descriptors are need to evaluate the preformulation risk classes, the

models resulted easy to use and characterized by high throughput^[42].

REFERENCES

1. Technical Monograph No.4, IDMA-APA Guideline, Pharmaceutical Preformulation Analytical Studies.
2. Raviolo MA, Briñón MC. Preformulation Studies of Zidovudine Derivatives: Acid Dissociation Constants, Differential Scanning Calorimetry, Thermogravimetry, X-Ray Powder Diffractometry and Aqueous Stability Studies. *Sci Pharm*. 2011 Sep; 79(3):479-491.
3. Sassi AB, Bunge KE, Hood BL, Conrads TP, Cole AM, Gupta P, Rohan LC. Preformulation and stability in biological fluids of the retrocyclin RC-101, a potential anti-HIV topical microbicide. *Res Ther*. 2011 Jul 29; 8:27.
4. Agashe H, Lagisetty P, Sahoo K, Bourne D, Grady B, Awasthi. Liposome-encapsulated EF24-HPβCD inclusion complex: a preformulation study and biodistribution in a rat model, *J Nanopart Res*. 2011 Jun 1; 13(6):2609-2623.
5. Sigfridsson K, Lundqvist R, Ohlson K. Preformulation evaluation of AZD1305, an oxabispidine intended for oral and intravenous treatment. *Drug Dev Ind Pharm*. 2011 Jun 27.
6. Huang M, Horwitz TS, Zweiben C, Singh SK. Impact of extractable/leachables from filters on stability of protein formulations. *J Pharm Sci*. 2011 Jun 21. doi: 10.1002/jps.22670.
7. Rahman Z, Agarabi C, Zidan AS, Khan SR, Khan MA. Physico-mechanical and stability evaluation of carbamazepine cocrystal with nicotinamide. *AAPS PharmSciTech*. 2011 Jun; 12(2):693-704.
8. Lilletvedt M, Smistad G, Tønnesen HH, Høgset A, Kristensen S. Solubilization of the novel anionic amphiphilic photosensitizer TPCS 2a by nonionic Pluronic block copolymers. *Eur J Pharm Sci*. 2011 Jun 14; 43(3):180-7.
9. Pandya S, Verma RK, Misra A. Nanoparticles containing nitric oxide donor with antileishmanial agent for synergistic effect against visceral leishmaniasis, *J Biomed Nanotechnol*. 2011 Feb; 7(1):213-5.

10. Holm R, Jørgensen EB, Harborg M, Larsen R, Holm P, Müllertz A, Jacobsen J. A novel excipient, 1-perfluorohexyloctane shows limited utility for the oral delivery of poorly water-soluble drugs - Preformulation, *Eur J Pharm Sci.* 2011 Mar 18; 42(4):416-22.
11. Malaj L, Censi R, Capsoni D, Pellegrino L, Bini M, Ferrari S, Gobetto R, Massarotti V, Di Martino P.. Characterization of nicergoline polymorphs crystallized in several organic solvents. *J Pharm Sci.* 2011 Jul; 100(7):2610-22.
12. Dutta AK, Stodghill SP, Wyandt CM. Physicochemical characterization of NPC 1161C, a novel antimalarial 8-aminoquinoline, in solution and solid state. *AAPS PharmSciTech.* 2011 Mar; 12(1):177-91.
13. Agatonovic-Kustrin S, Morton DW, Worthington MS, Glass BD. Modeling the effect of selected cyclodextrins on nifedipine solubility. *Curr Drug Discov Technol.* 2011 Jun 1;8(2):146-54.
14. Soares-Sobrinho JL, de La Roca Soares MF, Lopes PQ, Correia LP, de Souza FS, Macêdo RO, Rolim-Neto PJ. A preformulation study of a new medicine for Chagas disease treatment: physicochemical characterization, thermal stability, and compatibility of benznidazole. *AAPS PharmSciTech.* 2010 Sep; 11(3):1391-6.
15. Mortko CJ, Sheth AR, Variankaval N, Li L, Farrer BT. Risk assessment and physicochemical characterization of a metastable dehydrate API phase for intravenous formulation development, *J Pharm Sci.* 2010 Dec;99(12):4973-81.
16. Wischke C, Zhang Y, Mittal S, Schwendeman SP. Development of PLGA-based injectable delivery systems for hydrophobic fenretinide. *Pharm Res.* 2010 Oct; 27(10):2063-74.
17. Hughey JR, DiNunzio JC, Bennett RC, Brough C, Miller DA, Ma H, Williams RO 3rd, McGinity JW. Dissolution enhancement of a drug exhibiting thermal and acidic decomposition characteristics by fusion processing: a comparative study of hot melt extrusion and KinetiSol dispersing . *AAPS PharmSciTech.* 2010 Jun;11(2):760-74.
18. Jensen JS, Wertz CF, O'Neill VA. Upsher-Smith Laboratories, Inc, 6701 Evenstad Drive, Maple Grove. Preformulation stability of trans-resveratrol and trans-resveratrol glucoside (Piceid). *J Agric Food Chem.* 2010 Feb 10; 58(3):1685-90.
19. Hageman MJ. Preformulation designed to enable discovery and assess developability. *Comb Chem High Throughput Screen.* 2010 Feb;13(2):90-100.
20. Eppler A, Weigandt M, Hanefeld A, Bunjes H. Merck Serono, Relevant shaking stress conditions for antibody preformulation development. *Eur J Pharm Biopharm.* 2010 Feb;74(2):139-47.
21. Dinunzio JC, Brough C, Hughey JR, Miller DA, Williams RO 3rd, McGinity JW. Fusion production of solid dispersions containing a heat-sensitive active ingredient by hot melt extrusion and Kinetisol dispersing. *Eur J Pharm Biopharm.* 2010 Feb;74(2):340-51.
22. Kuehl PJ, Stratton SP, Powell MB, Myrdal PB. Preformulation, formulation, and in vivo efficacy of topically applied apomine. *Int J Pharm.* 2009 Dec 1;382(1-2):104-10.
23. Aguilar-Díaz JE, García-Montoya E, Pérez-Lozano P, Suñe-Negre JM, Miñarro M, Ticó JR. The use of the SeDeM Diagram expert system to determine the suitability of diluents-disintegrants for direct compression and their use in formulation of ODT. *Eur J Pharm Biopharm.* 2009 Nov; 73(3):414-23.
24. Hulse WL, Forbes RT, Bonner MC, Getrost M. The characterization and comparison of spray-dried mannitol samples. *Drug Dev Ind Pharm.* 2009 Jun; 35(6):712-8.
25. Bee JS, Chiu D, Sawicki S, Stevenson JL, Chatterjee K, Freund E, Carpenter JF, Randolph TW. Monoclonal antibody interactions with micro- and nanoparticles: adsorption, aggregation, and accelerated stress studies. *J Pharm Sci.* 2009 Sep;98(9):3218-38.
26. Zakeri-Milani P, Barzegar-Jalali M, Azimi M, Valizadeh H. Biopharmaceutical classification of drugs using intrinsic dissolution rate (IDR) and rat intestinal permeability. *Eur J Pharm Biopharm.* 2009 Sep; 73(1):102-6.

27. Hirlekar R, Kadam V. Preformulation study of the inclusion complex irbesartan-beta-cyclodextrin. *AAPS PharmSciTech.* 2009;10(1):276-81.
28. Zeng Y, Fan H, Chiueh G, Pham B, Martin R, Lechuga-Ballesteros D, Truong VL, Joshi SB, Middaugh CR. Towards development of stable formulations of a live attenuated bacterial vaccine: a preformulation study facilitated by a biophysical approach. *Hum Vaccin.* 2009 May;5(5):322-31.
29. Zhang SQ, Rahman Z, Thumma S, Repka MA, Chen GH, Li SM. Development and evaluation of a pH-dependent sustained release tablet for irritable bowel syndrome. *Drug Dev Ind Pharm.* 2009 Jan; 35(1):57-64.
30. Chatted IS. Studies on development of insoluble drugs as pharmaceutical suspensions by response surface methodology. *Pharmazie.* 2008 Oct;63(10):726-30.
31. Corti G, Maestrelli F, Cirri M, Mura P, Zerrouk N. Dissolution and permeation properties of naproxen from solid-state systems with chitosan. *Drug Deliv.* 2008 Jun; 15(5):303-12.
32. Thumma S, Majumdar S, Elsohly MA, Gul W, Repka MA. Preformulation studies of a prodrug of Delta9-tetrahydrocannabinol. *AAPS PharmSciTech.* 2008;9(3):982-90.
33. Gao K, Sun J, Liu K, Liu X, He Z. Preparation and characterization of a submicron lipid emulsion of docetaxel: submicron lipid emulsion of docetaxel. *Drug Dev Ind Pharm.* 2008 Nov; 34(11):1227-37.
34. Schilling SU, Bruce CD, Shah NH, Malick AW, McGinity JW. Citric acid monohydrate as a release-modifying agent in melt extruded matrix tablets. *Int J Pharm.* 2008 Sep 1; 361(1-2):158-68.
35. Mutalik S, Manoj K, Reddy MS, Kushtagi P, Usha AN, Anju P, Ranjith AK, Udupa N. Chitosan and enteric polymer based once daily sustained release tablets of aceclofenac: in vitro and in vivo studies. *AAPS PharmSciTech.* 2008; 9(2):651-9.
36. Chrzanowski F. Preformulation considerations for controlled release dosage forms. Part II. Selected candidate support. *AAPS PharmSciTech.* 2008;9(2):639-45.
37. Sanghvi R, Mogalian E, Machatha SG, Narazaki R, Karlage KL, Jain P, Tabibi SE, Glaze E, Myrdal PB, Yalkowsky SH. Preformulation and pharmacokinetic studies on antalarmin: a novel stress inhibitor. *J Pharm Sci.* 2009 Jan; 98(1):205-14.
38. Dhiman M, Yedurkar P, Sawant KK. Formulation, characterization, and in vitro evaluation of bioadhesive gels containing 5-Fluorouracil. *Pharm Dev Technol.* 2008;13(1):15-25.
39. Dong Y, Ng WK, Surana U, Tan RB. Solubilization and preformulation of poorly water soluble and hydrolysis susceptible N-epoxymethyl-1,8-naphthalimide (ENA) compound. *Int J Pharm.* 2008 May 22; 356(1-2):130-6.
40. Salnikova MS, Joshi SB, Rytting JH, Warny M, Middaugh CR. Preformulation studies of *Clostridium difficile* toxoids A and B. *J Pharm Sci.* 2008 Oct;97(10):4194-207.
41. Sipos P, Szucs M, Szabó A, Eros I, Szabó-Révész P. An assessment of the interactions between diclofenac sodium and ammonio methacrylate copolymer using thermal analysis and Raman spectroscopy. *J Pharm Biomed Anal.* 2008 Jan 22; 46(2):288-94.
42. Crivori P, Morelli A, Pezzetta D, Rocchetti M, Poggesi I. Development and validation of in silico models for estimating drug preformulation risk in PEG400/water and Tween80/water systems. *Eur J Pharm Sci.* 2007 Nov; 32(3):169-81.