LITERATURE REVIEW
2.1 Patent Search

Patent / Application Number, Name of Patent Holder

US PATENT

Samuels; Glenn J. (Sunnyvale, CA), Lee; Jung-Chung (San Jose, CA), Lee; Charles (Union City, CA), Berry; Stephen (Saratoga, CA), Jarosz; Paul J. (Los Altos, CA)

October 3, 1995

High dose formulation

A method for manufacturing a pharmaceutical formulation having an active agent selected from the group consisting of mycophenolate mofetil and its acid, comprising the steps of: liquefying the active agent by heating it to a first temperature above its melting point; cooling said liquefied active agent to a second temperature below its melting point, at which second temperature said active agent remains liquefied; and filling said liquefied active agent into a pharmaceutical dosage form.

A method for manufacturing a pharmaceutical formulation having the mycophenolate mofetil as an active agent comprising the steps of: liquefying the mycophenolate mofetil by heating it to a temperature of about 95 °C to 120 °C; admixing croscarmellose sodium, in an amount sufficient to serve as a disintegrant in said formulation when finished, with said liquefied model drug; cooling said admixed liquefied mycophenolate mofetil and croscarmellose sodium to a temperature below about 80 °C; and filling said cooled, liquefied the mycophenolate mofetil admixed with croscarmellose sodium into hard or soft gelatin capsules.
US PATENT

Use of granular materials based on pyrogenically produced silicon dioxide in pharmaceutical compositions

Use of a granular material based on pyrogenically produced silicon dioxide in a pharmaceutical composition. Pharmaceutical composition containing a granular material based on pyrogenically produced silicon dioxide and at least one pharmaceutical active constituent. Adsorbate of a granular material based on pyrogenically produced silicon dioxide and at least one further substance selected from pharmaceutical active constituents and auxiliary substances.

WO PATENT

Solid formulations containing trehalose

The patent application published with 27 claims of which 3 are independent.

A method of making solid formulations comprising the steps of:

a) combining components comprising an amount of trehalose sufficient to act as an effective diluent in the formulations formed and an amount of an active agent such that each dosage form formed contains an effective amount of active agent and an amount of solvent sufficient to suspend or dissolve the trehalose and active agent;

b) processing the product of step a) to form a powder, pellets, granules or microgranules comprising a substantially homogeneous mixture of the components; and

c) forming formulations from the powder, granules or microgranules.
WO PATENT

Oral formulation

A composition comprising

(i) an immunosuppressant,

(ii) at least one compound selected from tocopherol, tocotrienol and the derivatives thereof,

(iii) a short chain phospholipid and

(iv) a non-ionic surfactant.

US PATENT

Crystalline anhydrous mycophenolate mofetil and intravenous formulation thereof

A crystalline anhydrous salt consisting essentially of the mycophenolate mofetil complexed with an anion selected from the group consisting of chloride, sulfate, phosphate and acetate.

2.2 Literature Search


Proquazone, a poorly wettable compound, was used as a model drug in the search for reasons to develop a capsule or tablet formulation. The capsules were filled with proquazone as active ingredient, with lactose monohydrate (200 mesh) as filler and with magnesium stearate as lubricant. The tablet was made out of a granulate as internal phase which consisted of proquazone as active ingredient, lactose as filler, corn starch as disintegrant and PVP as a binding agent. The external phase consisted of magnesium stearate and corn starch. The concentration of proquazone in the capsule and in the tablet formulation was varied. The capsule formulations showed a significantly slower dissolution of the drug substance than the tablet formulations especially for a high-drug load. Independently of the drug load, only the tablet formulation showed a high-
dissolution rate. Thus, concerning drug load, only the tablet formulations showed to be robust. It became clear that proquazone needs to be formulated as a granulate or a tablet to achieve a fast dissolution rate. Thus, a poorly wettable drug, especially when it is found in high concentrations, can have direct impact on the decision to develop a tablet or a capsule formulation.

M. Reus-Medina et al. (2004)

This study compares the compression behaviour of a new cellulose-based tableting excipient, hereinafter referred to as UICEL-A/102, and Avicel PH-102, a commercial direct compression excipient commonly referred to as microcrystalline cellulose (MCC). UICEL-A/102 shows the cellulose II lattice, while Avicel PH-102 belongs to the cellulose I polymorphic form. The median particle diameters of UICEL-A/102 and Avicel PH-102 fractions used in the study were 107 and 97 μm, respectively. Compared with Avicel PH-102, UICEL-A/102 was denser; the relative poured and tapped densities were: 0.277 and 0.327 (vs 0.195 and 0.248 for Avicel PH-102), respectively. The true density, ρtrue, of the two materials was comparable (~1.56 g cm⁻³). The slopes of the in-die and out-of-die Heckel curves for Avicel PH-102 were steeper than for UICEL-A/102. The relative density versus applied pressure plot was in good agreement with the modified Heckel equation. The out-of-die and in-die minimal pressure susceptibility (κ_min) values calculated were 3.36 × 10⁻³ and 8.09 × 10⁻³ MPa⁻¹ for UICEL-A/102 and 8.00 × 10⁻³ and 16.12 × 10⁻³ MPa⁻¹ for Avicel PH-102, respectively. The elastic recovery profiles showed UICEL-A/102 to be more elastic than Avicel PH-102. In conclusion, UICEL-A/102 and Avicel PH-102 differ in their compression behaviour under pressure. The different polymorphic forms could provide a possible explanation.

The aim of this work by Le VNP et al was to study the impact of the process on drug particle size. They chose ibuprofen, practically insoluble in water, as granulometry greatly influences its dissolution rate. They developed an original method using a laser granulometer to assess the size of ibuprofen within a blend before and after granulation and then compression. Wet granulation was performed with a Lodige and a Diosna granulator. The granules were then compressed. The evolution of ibuprofen particle size after these operations was checked. Two grades of ibuprofen differing in size were studied: ibuprofen 25 and ibuprofen 50.

After the wet granulation of ibuprofen 50 with a Lodige or a Diosna granulator, a decrease in size was observed. This could be caused by shocks occurring in the granulator. On the other hand, after compression of the granules, ibuprofen particle size increased and was greater than that measured before granulation. Compression could induce some fragmentation of ibuprofen associated with the plastic deformation and then, under pressure, a closeness of the fragments or deformed particles which could bind or associate with one another because the melting point of ibuprofen is not very high.

In the case of ibuprofen 25, the same phenomena were observed after compression. But, after granulation, particle size was not modified. There was little breaking of ibuprofen particles in the granulator because they are much smaller than those of ibuprofen 50.

This work shows the impact of the process on drug particle size when producing tablets. The method developed made it possible to differentiate and measure the size of ibuprofen particles in a blend.

The purpose of this study by Herder J et.al was to investigate the water granulation mechanism of the hydrophilic matrix polymer HPMC in a high shear mixer and to relate the properties of the granules and tablets to the molecular weight and the degree of substitution for eight HPMC grades. Although the hydrophilic matrix system is a well known drug delivery one, there is a difficulty in that the desirable water granulation technique often causes problems in the presence of relatively large amounts of HPMC due to its hydrophilicity. The results of this study show that the properties of the granules and the tablets fall into two groups according to whether the molecular weight of the polymer is high or low. The granules of low molecular weight were smaller and more compact, with better flow properties but with less tensile strength of the compacts, whereas the opposite was valid for granules of high molecular weight. The explanation for these differences is linked to the proposed granulation mechanism of HPMC, in which the properties of the gel layer are important. The dominant factors governing the properties are the molecular weight and, to lesser extent, the degree of substitution.

Wei H et.al (2006)

The purpose of this study was to predict the oral absorption of glyburide. Biorelevant dissolution methods, combined with permeability measurements and computational simulations, were used to predict the oral absorption of glyburide. The objective was to establish in vitro in vivo correlations (IVIVCs) based on the biopharmaceutics drug classification system. The solubility of the glyburide powder was measured in different media. The dissolution behavior of two commercial tablet formulations was tested in different media. Two chemical grades of sodium taurocholate: low quality (LQ) = crude and high quality (HQ) = 97% purity, and egg-lecithin: LQ = 60% and HQ = 99.1% purity were used to prepare fasted state small intestinal fluid (FaSSIF). Simulated intestinal fluid
(SIF) and blank FaSSIF without lecithin and taurocholate (BL-FaSSIF) were used as controls. The dissolution tests were performed under constant pH and dynamic pH conditions. The dynamic pH range from 5.0 to 7.5 simulated the biological pH range of gastrointestinal (GI) tract in the fasted state. The drug permeability was studied using Caco-2 cell line. The predictions of the fraction dose absorbed were performed using GastroPlus™. The results of the simulations were compared with actual clinical data taken from a bioequivalence study. The solubility of glyburide was highest in LQ-FaSSIF. The two tablet formulations had significantly different dissolution behaviors in LQ-FaSSIF. The in vitro data was used as the input function into a simulation software. The dynamic LQ-FaSSIF dissolution data achieved the best prediction of the average AUC and $C_{\text{max}}$ of the clinically observed data. The present study shows that BCS based parameters combined with software simulations can be used to establish an IVIVC for glyburide. In vitro/in silico tools can potentially be used as surrogate for bioequivalence studies.

Kind M et al. (2005)

Kind M et al. applied experimental design methodology in the development and optimization of drug release methods. Diclofenac sodium (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid monosodium salt) was selected as a mycophenolate mofetil and Naklofen® retard prolonged release tablets, containing 100 mg of diclofenac sodium, were chosen as a model prolonged release system. On the basis of previous results, a three-level three-factorial Box–Behnken experimental design was used to characterize and optimize three physicochemical parameters, i.e. rotation speeds of the stirring elements, pH, and ionic strengths of the dissolution medium, affecting the release of diclofenac sodium from the tablets. The chosen dependent variables (responses) were a cumulative percentage of dissolved diclofenac sodium in 2, 6, 12 and 24 h. For estimation
of coefficients in the approximating polynomial function, the least square regression method was applied. Afterwards, the information about the model reliability was verified by using the analysis of variance (ANOVA). The estimation of model factors' significance was performed by Student's t-test. For investigation of the shape of the predicted response surfaces and for model optimization, the canonical analysis was applied. Their study proved that experimental design methodology could efficiently be applied for characterization and optimization of analytical parameters affecting drug release and that it is an economical way of obtaining the maximum amount of information in a short period of time and with the fewest number of experiments.

Lusina M et al (2005)

The purpose of stability testing is to investigate how the quality of a drug product changes with time under the influence of environmental factors, to establish a shelf life for the product and to recommend storage conditions. Stability study of losartan/hydrochlorothiazide tablets is presented in this paper. Losartan (angiotensin II receptor antagonist) and hydrochlorothiazide (diuretic) are successfully used in association in the treatment of hypertension. Stability study of losartan/hydrochlorothiazide tablets consisted of three steps: stress test (forced degradation study), preliminary testing (selection of packaging) and formal stability testing. The results of stress test suggested that losartan/hydrochlorothiazide tablets are sensitive to moisture. It was demonstrated that the developed analytical methods are stability indicating. Additional preliminary testing was performed in order to select appropriate packaging for losartan/hydrochlorothiazide tablets. OPA/Al/PVC//Al blisters were found to provide adequate protection for the product. Based on the first 12 months of the formal stability study, a shelf life of 24 months was proposed.
Losartan/hydrochlorothiazide tablets in OPA/Al/PVC/Al blisters are demonstrated to be chemically, physically and microbiologically stable.


The purpose of this audit was to examine the patterns of use, reported side effects and cost impact of the drug in the Clinical and Immunology and Allergy (CIA) unit of Australia's largest teaching hospital. Prescription patterns for the mycophenolate mofetil by consultant immunologists at Westmead hospital between 2000 and 2004 were obtained from the pharmacy. These data were sorted for non-S100 indications. A single immunologist then reviewed the patient files. We also reviewed the literature on the use of this promising immunosuppressant. There has been a marked increase in use of the mycophenolate mofetil since year 2000 by the Department of CIA. A total of 75 patients were prescribed the mycophenolate mofetil for non-S100 indications. Common indications were systemic lupus erythematosus, pemphigus vulgaris, chronic idiopathic urticaria, myasthenia gravis, polymyositis, atopic dermatitis, Sjogren's disease, uveitis and vasculitis. It is clear that the mycophenolate mofetil has potential for use in a number of immunological disorders because of its relatively benign side effect profile and observed efficacy. Double blinded, placebo-controlled, multicentre trials are necessary to establish its therapeutic role. Our study highlights some of the conditions for which this agent is useful.


Orelli JV et al used proquazone as a mycophenolate mofetil in the search for reasons to develop a capsule or tablet formulation. The capsules were filled with proquazone as active ingredient, with lactose monohydrate (200 mesh) as filler and with magnesium stearate as lubricant. The tablet was made out of a granulate as internal phase which consisted of proquazone as active ingredient, lactose as filler, corn starch as disintegrant
and PVP as a binding agent. The external phase consisted of magnesium stearate and corn starch. The concentration of proquazone in the capsule and in the tablet formulation was varied. The capsule formulations showed a significantly slower dissolution of the drug substance than the tablet formulations especially for a high-drug load. Independently of the drug load, only the tablet formulation showed a high-dissolution rate. Thus, concerning drug load, only the tablet formulations showed to be robust. It became clear that proquazone needs to be formulated as a granulate or a tablet to achieve a fast dissolution rate. Thus, a poorly wettable drug, especially when it is found in high concentrations, can have direct impact on the decision to develop a tablet or a capsule formulation.


Kukura J et.al used computational analysis to examine the hydrodynamic environment within the USP Apparatus II at common operating conditions. Experimental validation of the computational model shows that the simulations of fluid motion match the dispersion of dye observed in experiments. The computations are then used to obtain data that cannot be easily measured with experiments, specifically the distribution of shear forces within the media and along the wall. Results show that the shear environment is highly non-uniform. Increasing the paddle speed from 50 to 100 rpm does not improve shear homogeneity within the apparatus. Experiments show that this uneven distribution of hydrodynamic forces is a direct cause of dissolution testing variability. This variability is large enough to cause for type II dissolution test failures, i.e., failures are a result of a vulnerability of the testing method rather than a problem with a dosage form. Future development of new dissolution tests should include evaluations of the hydrodynamic environments to eliminate this potential source of failure that is unrelated to product quality.
Williams AC et al. (2004)

An active pharmaceutical ingredient (API) was found to dissociate from the highly crystalline hydrochloride form to the amorphous free base form, with consequent alterations to tablet properties. Here, a wet granulation manufacturing process has been investigated using in situ Fourier transform (FT)-Raman spectroscopic analyses of granules and tablets prepared with different granulating fluids and under different manufacturing conditions. Dosage form stability under a range of storage stresses was also investigated.

Despite the spectral similarities between the two drug forms, low levels of API dissociation could be quantified in the tablets; the technique allowed discrimination of around 4% of the API content as the amorphous free base (i.e. less than 1% of the tablet compression weight). API dissociation was shown to be promoted by extended exposure to moisture. Aqueous granulating fluids and manufacturing delays between granulation and drying stages and storage of the tablets in open conditions at 40 °C/75% relative humidity (RH) led to dissociation. In contrast, non-aqueous granulating fluids, with no delay in processing and storage of the tablets in either sealed containers or at lower temperature/humidity prevented detectable dissociation.

It was concluded that appropriate manufacturing process and storage conditions for the finished product involved minimizing exposure to moisture of the API. Analysis of the drug using FT-Raman spectroscopy allowed rapid optimization of the process whilst offering quantitative molecular information concerning the dissociation of the drug salt to the amorphous free base form.

This work by Crail DJ et al evaluated the use of a commercially available 200 ml vessel for dissolution of five drug products with various solubilities. Each of the five drug products (four with USP monographs and one proprietary tablet formulation) was run at four different conditions (USP 25 monograph, six dosage units in single 1 l vessel, 200 ml at the USP Monograph speed, and 200 ml at calculated paddle speed which matches the hydrodynamics of the USP vessel). Six dosage units in a single vessel were used as a comparison to increase the drug concentration for dissolution testing. Due to the different dissolution hydrodynamics, drug dissolution from the dosage forms was slower using the 200 ml conversion kit than when the USP method with a 1 l vessel was used. However, use of the 200 ml vessel at higher paddle speeds calculated by the power/volume equation, yielded similar results as the monograph method. Thus, it appears that using the power/volume ratio calculation to obtain comparable hydrodynamics lends utility to the 200 ml vessel as a means for characterizing the dissolution profile of low dose solid oral drug products. The results of the multiple dosage units per vessel also gave similar results to that of the USP monograph method.


Because several studies have revealed a relation between early graft rejection and long-term graft survival, potential benefits have been attributed to the model drug. The cost of the drug is, however, prohibitive, which renders its long-term use in countries with limited income. We thus compared the pharmacokinetic profiles of a new mycophenolate mofetil generic formulation (developed by Ivax CR) with those of innovator (Hoffman La Roche) in healthy volunteers. This open label, balanced randomized, two-treatment, two-period, two-sequence, single-dose, crossover, comparative oral bioavailability study was conducted in non-smoking adult male healthy volunteers between the ages of 18 and 45.
years. The study was performed in accordance with the basic principles defined in the US 21 CFR Part 312.20 and the principles enunciated in the Declaration of Helsinki (World Medical Association Declaration of Helsinki). The subjects were given a single oral 1 g dose with a washout period of 10 days. Pharmacokinetic profiles included blood levels at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 10, 12, 16, 20, 24, 30, 36, and 48 hours following each dose. The formulations were MMCept 500 mg tablets and Cellcept 500 mg tablets. Subjects were fasted overnight and for 4 hours postdosing. Mycophenolic acid (MPA) concentrations were determined using HPLC. Physical examinations, hematology, urinalysis, and serum chemistry tests including liver enzymes were performed at screening and at the end of the study. Subjects were monitored for safety and adverse events throughout the study. Both products showed similar bioavailability. The LSM were within the limits for FDA approval (80 to 125), suggesting that the two products are equivalent and switchable.

Mitchell SA et al. (2003)

The purpose of this study was to develop a technique to enhance the dissolution rate of poorly water-soluble drugs with hydroxypropyl methylcellulose (HPMC) without the use of solvent or heat addition. Three poorly water-soluble drugs, naproxen, nifedipine, and carbamazepine, were studied with low-viscosity HPMC USP Type 2208 (K3LV), HPMC USP Type 2910 (E3LV and E5LV), and methylcellulose. Polymer and drug were dry-blended, compressed into slugs on a tablet press or into ribbons on a roller compactor, and then milled into a granular powder. Dissolution testing of the milled powder was performed on USP Apparatus II, 100 rpm, 900 ml deionized water, 37 °C. Drug distribution vs. particle size was also studied. The compaction processes enhanced drug dissolution relative to drug alone and also relative to corresponding loosely mixed physical mixtures. The roller compaction and slugging methods produced comparable
dissolution enhancement. The mechanism for dissolution enhancement is believed to be a microenvironment HPMC surfactant effect facilitated by keeping the HPMC and drug particles in close proximity during drug dissolution. The compaction methods in this study may provide a lower cost, quicker, readily scalable alternative for formulating poorly water-soluble drugs.


This work describes a new approach to prepare a fast-release dosage form for carbamazepine (CBZ), involving the use of melt granulation process in high shear mixer for the production of tablets. In particular, the granules containing CBZ were prepared using polyethylene glycol (PEG) 4000 as a melting binder and lactose monohydrate as a hydrophilic filler. The potential of the intragranular addition of crospovidone as a dissolution enhancer and a disintegrant agent was also evaluated. After the analysis of their solid state performed by means of X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC), the granules were characterised from the technological and dissolution point of view. The subsequent step encompassed the preparation and the evaluation of the tablets, including the effect of the extragranular introduction of crospovidone. Besides the remarkable enhancement of drug dissolution rate of the granulates in comparison to physical mixtures and pure drug, no significant differences were found between the dissolution profiles of the granulates containing lactose or crospovidone. However, the difficult disintegration and bad dissolution performance of the tablets not containing intragranular crospovidone highlight the necessity of this disintegrant in the granulating mixture. Moreover, the extragranular addition of a small amount of crospovidone gave rise to a further amelioration of the disintegration and dissolution performances.

Accelerated stability studies are a common approach for predicting the long-term stability of pharmaceutical formulations. However, in this study, a slowing of dissolution was observed for a formulation following storage at elevated temperature and humidity. The moisture sorption isotherm for the binder, polyvinylpyrrolidone (PVP), shows absorption of a significant quantity of water on exposure to elevated humidity. Modulated temperature differential scanning calorimetry (mDSC) has been used to demonstrate that moisture uptake will depress the glass transition temperature ($T_g$) of PVP to the conditions used in accelerated stability studies. Exposure to elevated temperature and humidity resulted in a change in the PVP from the glassy to the rubbery state. This conversion produces a change in the dissolution profile. Long-term stability studies conducted at temperatures and humidity below the $T_g$ would not have induced this change.

Gil-Alegre ME et al (2001)

Gil-Alegre ME et al demonstrated that during the pharmaceutical development of a new drug, it is necessary to select as soon as possible the formulation with the best stability characteristics. The current International Commission for Harmonisation (ICH) regulations regarding stability testing requirements for a Registration Application provide the stress testing conditions with the aim of assessing the effect of severe conditions on the drug product. In practice, the well-known Arrhenius theory is still used to make a rapid stability prediction, to estimate a drug product shelf life during early stages of its pharmaceutical development. In this work, both the planning of a stress stability study to obtain a correct stability prediction from a temperature extrapolation and the suitable data treatment to discern the reliability of the stability results are discussed. The study was
focused on the early formulation step of a very stable drug, Mitonafide (antineoplastic agent), formulated in a parenteral solution and in tablets. It was observed, for the solid system, that the extrapolated results using Arrhenius theory might be statistically good, but far from the real situation if the stability study is not designed in a correct way. The statistical data treatment and the stress–stability test proposed in this work are suitable to make a reliable stability prediction of different formulations with the same drug, within its pharmaceutical development.

Roy J (2001)

The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. The International Conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. In this review, a description of different types and origins of impurities in relation to ICH guidelines and, degradation routes, including specific examples, are presented. The article further discusses measures regarding the control of impurities in pharmaceuticals.

Badawy SIF et.al (2000)

In this study by Badawy SIF et.al, various processing variables that can influence granulation characteristics of a lactose-based formulation were evaluated using a Plackett–Burman experimental design. These parameters were impeller speed, granulating solution addition rate, total amount of water added in the granulation step, wet massing time, moisture content of the granulation after drying, and screen size used for the dry milling. Results showed that granulation growth was enhanced by the increase in the amount of added water, high impeller speed, and short wet massing time. On the other hand, moisture content had the largest impact on granulation compressibility,
followed by the wet massing time and impeller speed. Increasing moisture content of the granulation and decreasing wet massing time or impeller speed increased granulation compressibility. Increasing impeller speed and/or wet massing time decreased granule porosity and fragmentation propensity, which led to decreased granulation compressibility. Granulation compressibility was extremely sensitive to processing conditions. Tablets from all runs showed acceptable weight variation and friability, suggesting that the parameters evaluated had little effect on these responses in the ranges tested.

Koparkar AD et al (1990)

Intrinsic dissolution rates were determined for different grades of commonly used calcium salt fillers and lactose. Typical tablet formulations of low-dose drugs were studied to determine the influence of this property on drug dissolution.

Goodhart FW et al (1973)

In this study by Goodhart FW et al, an in vitro technique for testing the disintegration and dissolution of tablets and capsules was developed and evaluated. The apparatus consists of a beaker with a cylindrical well in the bottom into which is placed a platform containing the dosage form to be tested. Shallow cylindrical depressions in the platform are used to hold capsules snugly in a vertical position for testing while variously shaped depressions are used for tablets, depending on their size and shape. Comparisons between the official and the new method indicated that the official test does not differentiate between capsule formulations containing a hydrophobic lubricant. A phenylpropanolamine hydrochloride capsule formulated with a high level of magnesium stearate was shown to release drug more slowly in vitro and in vivo. The effects of capsule formulation factors such as type and level of lubricant and disintegrant as well as
the presence of a surfactant were determined. It was found that the use of magnesium stearate and hydrogenated vegetable oil as lubricants significantly prolonged the *in vitro* disintegration time of hard gelatin capsules. Hard gelatin capsules also disintegrated more rapidly in artificial gastric fluid as compared to distilled water, and machine-filled capsules generally disintegrated more slowly than hand-filled capsules. Studies on tablets containing a slightly water-soluble drug indicated that the method of preparing the granulation has an important effect on the *in vitro* release of the drug.