3. REVIEW OF LITERATURE

Several investigations have been carried out in the past on IVIVC and method development for analyzing drugs in biological fluids. A survey of literature was carried out in such investigations. In what follows, some of the important investigations are discussed.

S. Dutta and coworkers\textsuperscript{28} have reported the once-a-day extended -release dosage form of Divalproex Sodium III: development and validation of a Level A \textit{in vitro} - \textit{in vivo} correlation (IVIVC). Defining a quantitative and reliable relationship between \textit{in vitro} drug release and \textit{in vivo} absorption is highly desired for rational development, optimization and evaluation of controlled-release dosage forms and manufacturing process. During the development of a once-daily extended-release (ER) tablet of divalproex sodium, a predictive \textit{in vitro} drug release method was designed and statistically evaluated using three formulations with varying release rates. In order to establish an internally and externally validated Level A IVIVC, a total of five different ER formulations of divalproex sodium were used to evaluate a linear IVIVC model based on the \textit{in vitro} test method. For internal validation, a single-dose four-way crossover study (N=16) was performed using fast-, medium- and slow-releasing ER formulations and a 12 h IV infusion of valproic acid as reference. To validate the IVIVC externally, a second three-way crossover study (N=36) was performed using slightly-fast-, medium- and slightly-slow-releasing ER formulations. The \textit{in vivo} absorption–time profile was inferred by deconvolution of the observed plasma concentration–time profiles against the unit disposition function (UDF). A linear IVIVC model was established in which the \textit{in vivo} absorption was expressed as a function of \textit{in vitro} drug release. Plasma profiles of ER formulations were estimated via convolution of \textit{in vitro} release profiles with the UDF. Successful internal and external validations of the model were demonstrated by individual and average absolute percent prediction errors of \(<9\%\) for both $C_{\text{max}}$ and $\text{AUC}_{\infty}$. In conclusion, a Level A IVIVC describing the
entire time-course of plasma concentrations was developed and validated, both internally and externally, for ER formulations of divalproex sodium.

S. Hayes and coworkers\textsuperscript{29} have reported on interpretation and optimization of the dissolution specifications for a modified release product with an \textit{In Vivo-In Vitro} Correlation (IVIVC). Almost invariably, the \textit{in vitro} dissolution test is interpreted in terms of bioequivalence. The literature that describes methods for setting \textit{in vitro} dissolution specifications is reviewed. The most common interpretation of these specifications is a deterministic one, that is, those batches passing the dissolution specifications would be bioequivalent with the reference if tested \textit{in vivo} and those failing the dissolution specifications would not be bioequivalent if tested \textit{in vivo}. Due to random variation, the deterministic interpretation is not appropriate. Instead, one need to consider the conditional probability that a batch that has passed the \textit{in vitro} dissolution test would demonstrate bioequivalence if tested \textit{in vivo}, and that a batch known to have failed the \textit{in vitro} dissolution test would demonstrate bioinequivalence if tested \textit{in vivo}. One way to estimate these probabilities is by means of a simulated experiment in which the production and testing (\textit{in vivo} and \textit{in vitro}) of a large number of batches is computer simulated. Such a simulation can only be performed if the relationship between the \textit{in vitro} dissolution characteristics and the \textit{in vivo} performance of the product has been modeled. These models are generally referred to as \textit{in vivo–in vitro} correlations (IVIVC). The results of one such experiment are described. The above-mentioned conditional probabilities are shown to depend on the choice of dissolution specifications. This result leads to the notion of optimal dissolution specifications. However, both of the conditional probabilities cannot be maximized simultaneously. The probability of making a correct decision on the basis of the \textit{in vitro} dissolution test is introduced as a possible optimality criterion. This probability is a linear combination of the two conditional probabilities of interest. Using this criterion, the optimal dissolution specifications can be found by searching over the multi dimensional space defined by the half width of each interval used in the specifications to find the
combination that maximizes this probability. This process is demonstrated using the Nelder-Mead search routine. The choice of dissolution specifications has profound implications for the routine production of the product because if the specifications were very narrow the probability of a batch passing would be low, resulting in a low hit rate. The same computer program used to perform the simulation experiment can be used to estimate the hit rate. Furthermore, it can be used to explore the magnitude of changes required in the parameters describing the test product (particularly variability) to increase a low hit rate to an acceptable level.

H. Kortesjarvi and coworkers\textsuperscript{30} have reported the Level A \textit{In Vitro - In Vivo} Correlation (IVIVC) model with Bayesian Approach to formulation Series. \textit{In vitro - in vivo} correlation (IVIVC) models for formulation series are useful in drug development, but the current models are limited by their inability to include data variability in the predictions. Goal was to develop a level A IVIVC model that provides predictions with probabilities. The Bayesian approach was used to describe uncertainty related to the model and the data. Three bioavailability studies of levosimendan were used to develop IVIVC model. Dissolution was tested at pH 5.8 with basket. The IVIVC model with Bayesian approach consisted of prior and observed data. All observed data were fitted to the one-compartment model together with prior data. Probability distributions of pharmacokinetic parameters and concentration time profiles were obtained. To test the external predictability of IVIVC model, only dissolution data of formulations E and F were used. The external predictability was good. The possibility to utilize all observed data when constructing IVIVC model, can be considered as a major strength of Bayesian approach. For levosimendan capsule data traditional IVIVC model was not predictable. The usefulness of IVIVC model with Bayesian approach was shown with the data, but the same approach can be used more widely for formulation optimization and for dissolution based biowaivers.

A. Savaser and coworkers\textsuperscript{31} have reported the preparation and \textit{in vitro} evaluation of sustained release tablet formulations of diclofenac sodium. The
effects of formulation variables on the release profile of diclofenac sodium (DS) from hydroxy propyl methyl cellulose (HPMC) and chitosan matrix tablets were studied. DS tablets were prepared by wet granulation and direct compression methods and different ratios of HPMC and chitosan were used. Physical properties of the prepared tablets and targeted commercial sustained release (SR) tablet and the drug release were studied in tablets that were placed in 0.1M HCl for 1 h and phosphate buffer solution was added to reach pH value of 7.5. In vitro studies showed that 20% HPMC contained SR formulation with direct (dry) compression method is the optimum formulation due to its better targeting profile in terms of release. This formulation also exhibited the best-fitted formulation into the zero order kinetics. The precision and accuracy of the analytical method were also checked. The repeatability and reproducibility of the method were also determined.

V.R.Uppoor\textsuperscript{32} has reported the regulatory perspectives on \textit{in vitro} (dissolution) / \textit{in vivo} (bioavailability) correlations. \textit{In vitro} dissolution has been extensively used as a quality control tool for solid oral dosage forms. In several cases, however, it is not known whether one can predict the \textit{in vivo} performance of these products from \textit{in vitro} dissolution data. In an effort to minimize unnecessary human testing, investigations of \textit{in vitro} / \textit{in vivo} correlations (IVIVC) between \textit{in vitro} dissolution and \textit{in vivo} bioavailability are increasingly becoming an integral part of extended release (ER) drug product development. This increased activity in developing IVIVCs indicates the value of IVIVCs to the pharmaceutical industry. Because of the scientific interest and the associated utility of IVIVC as a valuable tool, the US Food and Drug Administration has published Guidance in September 1997, entitled extended release oral dosage forms: development, evaluation and application of \textit{in vitro} / \textit{in vivo} correlations. A predictive IVIVC enables \textit{in vitro} dissolution to serve as a surrogate for \textit{in vivo} bioequivalence testing. IVIVCs can be used in place of bio studies that may otherwise be required to demonstrate bioequivalence, when certain pre approval and post approval changes are made in formulation, equipment, manufacturing process or in the manufacturing site. IVIVC development could
lead to improved product quality (more meaningful dissolution specifications) and decreased regulatory burden (reduced bio study requirements). FDA Guidance which deals with the development, evaluation methods, criteria and applications of IVIVCs. From a regulatory point of view, the applications of IVIVC to grant bio waivers and to set dissolution specifications for ER oral dosage forms are presented. Additionally, since the principles of IVIVC are considered to be similar for non-oral dosage forms, the guidance for oral extended release products may be applied for non-oral products as well. While the principles are likely to be the same, it is an interesting challenge to look at appropriate methods for dissolution testing and for development of \emph{in vitro / in vivo} correlations for products such as injectable depot formulations.

J. Emami and coworkers\cite{33} have reported the \emph{in vitro - in vivo} evaluation of sustained-release lithium carbonate (LC) matrix tablets: influence of hydrophilic matrix materials. Sustained-release matrix tablets were developed using different types and ratios of polymers including carbomer (CP), Na carboxy methyl cellulose (Na CMC) and hydroxy propyl methyl cellulose (HPMC), to assess the release profiles and \emph{in vivo} performance of the formulations. The tablets were prepared by either direct compression (DC) or wet granulation (WG). In the DC method, 69\% (450 mg) LC, 5, 10 or 15\% CP or Na CMC (of total tablet weight), lactose and /or Avicel (to maintain constant tablet weight) were mixed and directly compressed. In the WG method, 450 mg LC and 10, 20, or 30\% HPMC were granulated with Eudragit S100 solution, dried and then compressed to formulate the tablets. \emph{In vitro} and \emph{in vivo}, newly formulated sustained-release LC tablets were compared with sustained-release commercial tablets. \emph{In vivo} studies were conducted in nine healthy subjects in a cross-over design, with a 3x3 latin square sequence and pharmacokinetic parameters were estimated using classical methods.

V.H. Sunesen and coworkers\cite{34} have reported the \emph{in vivo in vitro} correlations for a poorly soluble drug, danazol, using the flow-through dissolution method with bio relevant dissolution media. The purpose of the study was to design dissolution tests that were able to distinguish between the
behavior of danazol under fasted and fed conditions, by using bio relevant media. In vitro dissolution of 100 mg danazol capsules was performed using the flow-through dissolution method. Flow rates were 8, 16 or 32 ml/min, corresponding to total volumes dissolution medium of 960, 1920 and 3840 ml, respectively. The media used contained bile salt and phospholipid levels relevant for either fasted or fed conditions in vivo. Crude and inexpensive bile components, porcine bile extract and soybean phospholipids, were used as the bile source. The effect of adding different concentrations and molar ratios of mono glycerides and fatty acids to the fed state media was investigated. In vivo release profiles under fasted and fed conditions were obtained from a previous study by deconvolution. In the fasted state, the physiologically most relevant correlation with in vivo results was achieved with a medium containing 6.3 mM bile salts and 1.25 mM phospholipids (8 ml/min). A medium containing 18.8 mM bile salts, 3.75 mM phospholipids, 4.0 mM mono glycerides and 30 mM fatty acids (8 ml/min) gave the closest correlation with fed state in vivo results. By using the flow-through dissolution method it was possible to obtain correlations with in vivo release of danazol under fasted and fed conditions. Both hydrodynamics and medium composition were important for the dissolution of danazol. In the fed state an IVIVC could only be obtained by including mono glycerides and fatty acids in the medium.

J.B. Dressman and coworker\textsuperscript{35} have reported the in vitro – in vivo correlations for lipophilic, poorly water-soluble drugs. Although several routes of administration can be considered for new drug entities, the most popular remains the oral route. To predict the in vivo performance of a drug after oral administration from in vivo data, it is essential that the limiting factor to absorption can be modelled in vitro. In the case of BCS class II drugs dissolution is rate-limiting to absorption, so the use of bio relevant dissolution tests can be used to predict differences in bioavailability among different formulations and dosing conditions. To achieve an a priori correlation, the composition, volume and hydrodynamics of the contents in the gastrointestinal lumen following administration of the dosage form must be accurately simulated. Four media
have been chosen/developed to model composition of the gastric and intestinal contents before and after meal intake. These are SGF, milk, FASSIF and FESSIF, which model fasted and fed state conditions in the stomach and small intestine respectively. Using these media, excellent correlations have been obtained with the following poorly soluble drugs: danazol, ketoconazole, atovaquone and troglitazone. In all cases, fed vs. fasted state effects can be predicted from dissolution data and where several formulations were available for testing, dissolution tests could also be used to determine which would have the best in vivo performance.

F. Langenbucher has reported on handling of computational in vitro/in vivo correlation problems by Microsoft Excel: IV. Generalized matrix analysis of linear compartment systems. A linear system comprising n compartments is completely defined by the rate constants between any of the compartments and the initial condition in which compartment(s) the drug is present at the beginning. The generalized solution is the time profiles of drug amount in each compartment, described by poly exponential equations. Based on standard matrix operations, an Excel worksheet computes the rate constants and the coefficients, finally the full time profiles for a specified range of time values.

R.Y. Cheung and coworkers have reported a new approach to the in vivo and in vitro investigation of drug release from loco regionally delivered microspheres. The purpose of this work was to determine the in vivo release profile of doxorubicin (Dox) delivered loco regionally by dextran-based microspheres (MS) and to develop an in vitro method for predicting in vivo drug release from MS— In Vitro-In Vivo correlation (IVIVC). For the determination of in vivo Dox release, drug-loaded MS were placed into hollow fibers (HF) and implanted subcutaneously into C3H mice. Samples were retrieved at various times following implantation, MS removed from HF and the amount of Dox remaining determined via ultraviolet/visible (UV/Vis) spectrophotometry. Various in vitro systems were designed and investigated for their ability to link in vivo and in vitro release profiles, including an open system (e.g. a column) with continuous flow of release medium at different flow rates and closed
systems (e.g. a cuvette) using different release media and conditions. About 34% of loaded Dox was released from MS in vivo at 48 h. Only an incremental release was observed over the ensuing 72 h. The release kinetics of Dox from MS using three of the investigated in vitro systems, column system and HF immersed in a buffer solution or growth medium gave release profiles that were highly correlated with the in vivo release profile ($r^2>9$). The relationships, both linear and non-linear, suggest that Level A IVIVC models can be developed for Dox release from loco regionally delivered MS using specially designed release systems.

B. De Spiegeleer and coworkers\textsuperscript{38} have reported the dissolution stability and IVIVC investigation of a buccal tablet. Using a recently developed bending point criterion to describe certain dissolution profiles, a physical stability screening study of a muco adhesive buccal tablet was performed in order to obtain a fast and useful in vitro testing system that allows the assessment of the physical stability of new formulations in a much faster way compared to the standard formal stability tests in which it takes months before conclusions can be drawn. The obtained dissolution results at normal, accelerated and stress conditions are correlated with each other, resulting in a rapid test system to evaluate the physical stability of the tablets. Last, a significant in vivo in vitro correlation (IVIVC) was established between the in vivo residence time in the buccal cavity and the in vitro bending point obtained from the dissolution data. For this particular case study, it is concluded that around 50% of the in vivo variability of the residence time in the mouth is explained by the in vitro bending point.

K.D. Vlugt-Wensink and coworkers\textsuperscript{39} have reported the pre clinical and clinical in vitro in vivo correlation of an hGH dextran microsphere formulation. The purpose was to investigate the in vitro in vivo correlation of a sustained release formulation for human growth hormone (hGH) based on hydroxyl ethyl methacrylated dextran (dex-HEMA) microspheres in Pit-1 deficient Snell dwarf mice and in healthy human volunteers. A hGH-loaded microsphere formulation was developed and tested in Snell dwarf mice (pharmacodynamic study) and in
healthy human volunteers (pharmacokinetic study). Single subcutaneous administration of the microspheres in mice resulted in a good correlation between hGH released in vitro and in vivo effects for the hGH-loaded microsphere formulation similar to daily injected hGH indicating a retained bioactivity. Testing the microspheres in healthy volunteers showed an increase (over 7–8 days) in hGH serum concentrations (peak concentrations: 1–2.5 ng/ml). A good in vitro in vivo correlation was obtained between the measured and calculated (from in vitro release data) hGH serum concentrations. Moreover, an increased serum concentration of biomarkers (insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3) was found again indicating that bioactive hGH was released from the microspheres. Good in vitro in vivo correlations were obtained for hGH-loaded dex-HEMA microspheres, which is an important advantage in predicting the effect of the controlled drug delivery product in clinical situations.

Y.Wang and coworker have reported the bias in the Wagner–Nelson estimate of the fraction of drug absorbed. The purpose was to examine and quantify bias in the Wagner-Nelson estimate of the fraction of drug absorbed resulting from the estimation error of the elimination rate constant (k), measurement error of the drug concentration and the truncation error in the area under the curve. Bias in the Wagner-Nelson estimate was derived as a function of post-dosing time (t), k, ratio of absorption rate constant to k (r) and the coefficient of variation for estimates of k (CVk), or CV% for the observed concentration, by assuming a one-compartment model and using an independent estimate of k. The derived functions were used for evaluating the bias with r = 0.5, 3, or 6; k = 0.1 or 0.2; CV, = 0.2 or 0.4; and CV, =0.2 or 0.4; for t = 0 to 30 or 60. Estimation error of k resulted in an upward bias in the Wagner-Nelson estimate that could lead to the estimate of the fraction absorbed being greater than unity. The bias resulting from the estimation error of k inflates the fraction of absorption versus time profiles mainly in the early post-dosing period. The magnitude of the bias in the Wagner-Nelson estimate resulting from estimation error of k was mainly determined by CV. The bias in the
Wagner-Nelson estimate resulting from estimation error in $k$ can be dramatically reduced by use of the mean of several independent estimates of $k$, as in studies for development of an in vivo - in vitro correlation. The truncation error in the area under the curve can introduce a negative bias in the Wagner-Nelson estimate. This can partially offset the bias resulting from estimation error of $k$ in the early post-dosing period. Measurement error of concentration does not introduce bias in the Wagner-Nelson estimate. Estimation error of $k$ results in an upward bias in the Wagner-Nelson estimate, mainly in the early drug absorption phase. The truncation error in AUC can result in a downward bias, which may partially offset the upward bias due to estimation error of $k$ in the early absorption phase. Measurement error of concentration does not introduce bias. The joint effect of estimation error of $k$ and truncation error in AUC can result in a non-monotonic fraction-of-drug-absorbed-versus-time profile. However, only estimation error of $k$ can lead to the Wagner-Nelson estimate of fraction of drug absorbed greater than unity.

G. Torrado and coworkers\textsuperscript{41} have reported the correlation of in vitro and in vivo acetaminophen availability from albumin micro aggregates oral modified release formulations. The aim of this study was to develop albumin micro aggregated oral formulations for controlled drug release and to reveal the possible influence of the release site on drug absorption. Acetaminophen was chosen as the model drug, which is included in the Class 1 group of the Biopharmaceutics Classification System (BCS). Albumin micro aggregates were formulated into tablets to obtain different drug release rates: Immediate Release (IR) tablets, multi particulate systems with an intermediate release rate and matrix systems showing slow release rate. The properties of the products were initially tested via dissolution studies and then via bioavailability studies in healthy volunteers. Controlled release albumin micro aggregated acetaminophen formulations for oral administration were obtained. The extent of drug absorption was comparable for all formulations, suggesting that the differences found in saliva concentration and urine cumulative profiles could be attributed merely to differences in drug release kinetics, as confirmed by the in
vitro–in vivo correlation study. Therefore, it can be concluded that extended release of acetaminophen does not influence its absorption via intestinal heterogeneity.

J.T. Dalton and coworkers\textsuperscript{42} have reported the predictive ability of Level A in vitro–in vivo correlation for ring cap controlled release acetaminophen tablets. The goal of this study was to establish and validate an in vitro-in vivo correlation (IVIVC) for two sustained-release formulations (a matrix tablet and a ring cap banded matrix tablet) containing 750 mg of acetaminophen. The in vitro dissolution and in vivo disposition of these formulations were examined by using a USP type III dissolution apparatus and a single-dose, three-way, crossover study that included an immediate-release acetaminophen dosage form, respectively. An IVIVC was established by using the mean fraction dissolved (FD) and mean fraction absorbed (FA) and used to simulate the plasma concentration-time profile of acetaminophen after administration of the matrix tablet (internal validation) and ring cap banded matrix tablet (external validation). A statistically significant relationship ($r^2 = 0.997, P < 0.001$) existed between the FD and FA for matrix tablets and was best described by the equation 

$\text{(FA)} = 0.984 \times \text{(FD)} + 0.0133$.

The percent predictions errors in $C_{\text{max}}$ and AUCL were $<10\%$ when predicting the plasma concentration-time profiles for the two formulations, validating the internal and external predictability of the IVIVC. The data (i) show that in vitro dissolution data are a good predictor of in vivo fraction absorbed for acetaminophen, (ii) support the general use of in vitro dissolution data for readily soluble and readily absorbed drugs, (iii) suggest that acetaminophen may serve as a model drug for evaluating novel sustained-release delivery systems, and (iv) provide a tangible example of the limitations of current methods for predicting and validating IVIVC.

H. Mahayni and coworkers\textsuperscript{43} have reported the evaluation of "external" predictability of an in vitro-in vivo correlation for an extended-release formulation containing metoprolol tartrate. The purpose of this study was to examine the external predictability of an in vitro-in vivo correlation (IVIVC) for a metoprolol hydrophilic matrix extended-release formulation, with an
acceptable internal predictability, in the presence of a range of formulation/manufacturing changes. In addition, this report evaluated the predictability of the IVIVC for another formulation of metoprolol tartrate differing in its release mechanism. Study 1 examined the scale up of a matrix extended-release tablet from a 3 kg small batch (I) to a 50 kg large batch (II). The second study examined the influence of scale and processing changes [3 kg small batch with fluid bed granulation and drying (III); 80 kg large batch with high shear granulation and microwave drying (IV) and a formulation with an alternate release mechanism formulated as a multi particulate capsule (V)]. In vitro dissolution of all formulations (I-V) was conducted with a USP apparatus I at pH 6.8 and 150 rpm. Subjects received the metoprolol formulations and serial blood samples were collected over 48 h and analyzed by a validated HPLC assay using fluorescence detection. A previously developed IVIVC was used to predict plasma profiles. Prediction errors (PE) were <10% for \( C_{\text{max}} \) and area under the curve (AUC) of concentration versus time for I, II and IV. The \( C_{\text{max}} \) for III was slightly underestimated (11.7%); however, the PE of the AUC was <10%. Formulation V displayed a PE for \( C_{\text{max}} \) > 20% and an AUC within 5% of observed values. The low PEs for \( C_{\text{max}} \) and AUC observed for I - IV strongly suggest that the metoprolol IVIVC is externally valid, predictive of alternate processing methods (IV), scale-up (II, III) and allows the in vitro dissolution data to be used as a surrogate for validation studies. However, the lack of predictability for V supports the contention that IVIVCs are formulation specific.

P. Veng Pedersen and coworkers\(^4^4\) have reported the carbamazepine level - A in vivo - in vitro correlation (IVIVC): a scaled convolution based predictive approach. A method is presented for prediction of the systemic drug concentration profile from in vitro release/dissolution data for a drug formulation. The method is demonstrated using four different tablet formulations containing 200 mg carbamazepine (CZM), each administered in a four way cross-over manner to 20 human subjects, with 15 blood samples drawn to determine the resulting concentration profile. Amount versus time dissolution data were obtained by a 75 rpm paddle method for each
formulation. Differentiation, with respect to time, of a monotonic quadratic spline fitted to the dissolution data provided the dissolution rate curve. The dissolution curve was through time and magnitude scaling mapped into a drug concentration curve via a convolution by a single exponential and the estimated unit impulse response function. The method was tested by cross-validation, where the in vivo concentration profiles for each formulation were predicted based on correlation parameters determined from in vivo-in vitro data from the remaining three formulations. The mean prediction error (MPE), defined as the mean value of 100% x (observed-predicted)/observed was calculated for all 240 cross-validation predictions. The mean values of MPE were in the range of 10-36% (average 22%) with standard deviations (S.D.s) in the range of 9-33% (average 13%), indicating a good prediction performance of the proposed in vivo - in vitro correlation (IVIVC) method.

G. Balan and coworkers\textsuperscript{45} have reported the In Vitro - In Vivo Correlation (IVIVC) models for metformin after administration of modified-release (MR) oral dosage forms to healthy human volunteers. The objective of the current study was to develop and evaluate the internal predictability for level C and A In Vitro-In Vivo Correlation (IVIVC) models for prototype modified-release (MR) dosage forms of metformin. In vitro dissolution data for metformin were collected for 22 h using a USP II (paddle) method. In vivo plasma concentration data were obtained from 8 healthy volunteers after administration of immediate-release (IR) and MR dosage forms of metformin. Linear level C IVIVC models were developed using dissolution data at 2.0 and 4.0 h and in vitro mean dissolution time (MDT). A deconvolution-based level A model was attempted through a correlation of percent in vivo input obtained through deconvolution and percent in vitro dissolution obtained experimentally. Further, basic and extended convolution level A IVIVC models were attempted for metformin. Internal predictability for the IVIVC models was assessed by comparing observed and predicted values for $C_{\text{max}}$ and AUC$_{\text{x}}$. The results suggest that highly predictive level C models with prediction errors (%PE) of <5% could be developed. Mean percent in vivo input for metformin was
incomplete from all formulations and did not exceed 35% of dose. The deconvolution-based level A models for all MR formulations were curvilinear. However, a unique IVIVC model applicable to all MR formulations could not be developed using the deconvolution approach. The basic convolution level A model, which used \textit{in vitro} dissolution as the \textit{in vivo} input, had %PE values as high as 103%. Using an extended convolution approach, which modeled the absorption of metformin using a Hill function, a level A IVIVC model with %PE as low as 11% was developed. The work indicates that level C and A IVIVC models with good internal predictability may be developed for a permeability- and absorption window-limited drug such as metformin.

N. Sirisuth and coworkers\textsuperscript{46} have reported the development and validation of a non-linear IVIVC model for a diltiazem extended release formulation. \textit{In vitro} dissolution of diltiazem capsules was examined using the following methods: USP Apparatus II (paddle) at 100 rpm and USP Apparatus III at 30 dpm. Seven healthy subjects received three diltiazem formulations (90 mg): slow (S), moderate (M), fast (F) releasing and an oral solution (90 mg). Serial blood samples were collected over 48 h and analyzed by a validated HPLC assay using ultraviolet detection. The $f_2$ metric (similarity factor) was used to analyze the dissolution data. Linear and non-linear (quadratic, cubic, and sigmoid functions) correlation models were developed using pooled fraction dissolved (FRD) and fraction absorbed (FRA) data from various combinations of the formulations. Predicted diltiazem concentrations were obtained by convolution of the \textit{in vivo} dissolution rates. Prediction errors were estimated for C\textsubscript{max} and AUC to determine the validity of the correlation. Apparatus II using purified water was found to be the most discriminating dissolution method. Significant intersubject (CV\%>50) was observed for C\textsubscript{max} and AUC. The quadratic M/F IVIVC model provided a significant relationship between FRD and FRA when using either two or three of the formulations. An average percent prediction error for C\textsubscript{max} and AUC for all formulations was 12.4% and 9.2\%, respectively. The prediction errors observed for C\textsubscript{max} and AUC
suggest that the predictability of the quadratic IVIVC model is inconclusive, as such, external validation studies are required.

O.A. Lake and coworkers\textsuperscript{47} have reported the \textit{in vitro} / \textit{in vivo} correlations of dissolution data of carbamazepine immediate release tablets with pharmacokinetic data obtained in healthy volunteers. The aim of the study was to select a dissolution test method for carbamazepine (CBZ) immediate release tablets, giving the best \textit{in vitro} / \textit{in vivo} correlations (IVIVC) and to determine the potential of this method as an estimate for bioequivalence testing. Four 200 mg CBZ products which are sold on the Dutch market, covering the innovator and three generic products were selected. They had been tested in a randomized, four way cross-over bioavailability study in healthy volunteers. Their dissolution rate behaviour \textit{in vitro} was investigated in two dissolution media: (1) 1\% sodium lauryl sulphate in water (SLS), in accordance with the United States Pharmacopeia (USP); (2) 0.1 mol/l Hydrochloric acid in water (HC). In the bioavailability study these products had shown no large differences in the extent of absorption (AUC\textsubscript{0-\textinfty}) but large differences in absorption rate. The products now also showed large differences in dissolution rate \textit{in vitro} in both dissolution media, the rank order being the same as for the absorption rate. It was concluded that the absorption rate \textit{in vivo} depends on the dissolution rate \textit{in vivo}. 'Level C' IVIVC according to the USP were optimized by plotting percentages dissolved on selected time points (D values) or their reciprocals (1/D values), against several pharmacokinetic parameters primarily related to the absorption phase and against AUC\textsubscript{0-\textinfty}. In this way for each IVIVC the optimum D or 1/D value, was calculated. For both media no meaningful IVIVC were obtained with AUC\textsubscript{0-\textinfty}, but favourable IVIVC were obtained with the parameters primarily related to the absorption phase. In the bioavailability study indicated above it was found that, among the pharmacokinetic characteristics primarily related to the absorption phase, C\textsubscript{max} is the most promising in expressing rate of absorption in bioequivalence testing in single dose studies with CBZ immediate release tablets. Consequently, C\textsubscript{max} was selected for expressing rate of absorption. The most favorable IVIVC were
obtained with D(20) in SLS versus C<sub>max</sub>. From this IVIVC and the requirements for bioequivalence AUC<sub>0-∞</sub>: 0.8-1.25 and C<sub>max</sub>: 0.75-1.35; 90% confidence interval), a specification for dissolution testing in SLS was calculated as follows: after 20 minutes, 34-99% dissolved. Owing to the fact that the rate of absorption <i>in vivo</i> depends on the dissolution rate <i>in vivo</i>, it can be concluded that with this specification bioequivalence with respect to both rate of absorption and extent of absorption is ensured. As this specification is comparable with the USP specification: not less than 75% dissolved after 1 h, it is concluded that the USP specification is suitable to ensure bioequivalence of CBZ immediate release tablets.

Natalie D Eddington has reported the <i>in vitro in vivo</i> correlation with metoprolol extended release tablets using two different releasing formulations: an internal validation evaluation. The objective of this analysis was to develop and validate internally an In Vitro In Vivo Correlation (IVIVC) for a hydrophilic matrix extended release metoprolol tablet using a combination of two formulations with different release rates. Three formulations of a hydrophilic matrix extended release tablets were manufactured to release metoprolol at a slow, moderate and fast rate. The <i>in vitro</i> dissolution methods utilized USP Apparatus II, pH 6.8 at 150 rpm. Seven healthy subjects received three metoprolol formulations (100 mg): slow, moderate and fast releasing and an oral solution (50 mg). Serial blood samples were collected over 48 h and analyzed by a validated HPLC assay using fluorescence detection. The f<sub>2</sub> metric (similarity factor) was used to analyze the dissolution data. Correlation models were developed using pooled fraction dissolved (FRD) and fraction absorbed (FRA) data from various combinations of two formulations (slow/moderate; moderate/fast and slow/fast). Predicted metoprolol concentrations were obtained by convolution of the <i>in vivo</i> dissolution rates. Prediction errors were estimated for C<sub>max</sub> and AUC to determine the validity of the correlation. An average percent prediction error for C<sub>max</sub> and AUC for all formulations of less than 12% was found for all IVIVC models. The relatively low prediction errors for C<sub>max</sub> and AUC observed strongly suggest that the metoprolol IVIVC models
with two formulations used in development are valid. Previous IVIVC with all three formulations was also found to be valid. The relatively low prediction error indicates that the correlations are predictive when using two or three formulations and allows the associated dissolution data to be used as a surrogate for bioavailability studies.

S. Takka and coworkers have reported the development and validation of an in vitro-in vivo correlation for buspirone hydrochloride extended release tablets. The aim of this study was to develop an In Vitro-In Vivo Correlation (IVIVC) for two buspirone hydrochloride extended release formulations and to compare their plasma concentrations over time with the commercially available immediate release (IR) tablets. In vitro release rate data were obtained for each formulation using the USP Apparatus 2, paddle stirrer at 50 and 100 rpm in 0.1 M HCl and pH 6.8 phosphate buffer. A three-way cross over study in 18 healthy subjects studied a 30 mg "Fast" (12 h) and 30 mg "Slow" (24 h) formulation of buspirone hydrochloride given once a day, and 2x15 mg immediate release tablets dosed at a 12 h interval. The similarity factor ($f_2$) was used to analyze the dissolution data. A linear correlation model was developed using percent absorbed data and percent dissolved data from the two formulations. Predicted buspirone hydrochloride concentrations were obtained by use of a curve fitting equation for the immediate release data to determine the volume of distribution and fraction absorbed constants. Prediction errors were estimated for $C_{\text{max}}$ and area under the curve (AUC) to determine the validity of the correlation. pH 6.8 at 50 rpm was found to be the most discriminating dissolution method. Linear regression analyses of the mean percentage of dose absorbed versus the mean in vitro release resulted in a significant correlation ($r^2>$0.95) for the two formulations. An average percent prediction error for $C_{\text{max}}$ was -0.16%, but was 16.1%, for the AUCs of the two formulations.

Korteja and coworkers have reported the development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules. The aim of this study was to investigate the possibility of developing different levels
of correlation between *in vitro* release and *in vivo* absorption rate for four modified-release levosimendan capsule formulations. Differences and similarities in the *in vitro* dissolution curves were compared with pharmacokinetic parameters describing absorption rate. Formulations F, G, H and I differed in the amounts of the delaying excipients alginic acid and HPMC. *In vitro* release rate was studied by the USP basket method using the following conditions: pH 5.8 or 7.4 and a rotation speed of 50 or 100 rpm. *In vivo* bioavailability was tested in nine healthy male volunteers and the fractions absorbed were calculated by the Wagner-Nelson method. Dissolution conditions pH 5.8 and a rotation speed of 100 rpm predicted best the similarities and differences in absorption rates among different formulations and levels C and B correlation coefficients were 0.85 and 0.97, respectively. For formulation H level A correlation \((r=0.997)\) was found when *in vitro* lag time was 0.2 h and time scale factor 1.9. This study indicated that dissolution tests developed can be used as a surrogate for human bioequivalence studies, for development processes of final commercial products, to ensure batch to batch bioequivalence and in the future in possible scale-up and post approval change cases for modified-release levosimendan formulation H.

Sajal kumar Saha and coworkers\(^5\) have reported the comparative *in vitro*-*in vivo* correlation analysis with pioglitazone tablets. *In vitro* release data were obtained for test and reference formulation using the USP paddle method (Apparatus 2) at 50 r/min and with the temperature of 37 °C in the dissolution medium of 0.1 mol/L hydrochloric acid of pH 1.2. Twelve healthy volunteers were administered both test and reference pioglitazone 30 mg tablet orally and blood samples were collected over 24 h period. *In vivo* drug concentrations were analyzed by a simple, fast and precise reverse phase binary HPLC method with UV detection to establish a correlation between *in vitro* release and *in vivo* absorption data. Similarity factor \((f_2)\) and dissimilarity factor \((f_1)\) were determined for the time intervals of 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 min and the obtained values were 65.17%, 59.37%, 63.62%, 66.61%, 68.89%, 70.73%, 72.27%, 73.59%, 74.65% and 75.67% for \(f_2\) and 9.43%, 9.00%, 5.42%, 3.86%, 3.57%, 2.45%, 2.08%, 1.82%, 1.62% and 1.45% for \(f_1\).
3.07%, 2.56%, 2.20%, 1.94%, 1.82% and 1.65% for f1 at respective time intervals. Mean dissolution time for test and reference products were obtained at 3.06 and 3.40 min respectively. f2 and f1 values obtained were within the acceptable range f2 (50%-100%) and f1 (<15%). Comparison of dissolution profiles corroborate that the test and reference formulations are similar and there is no linear in vitro-in vivo correlation.

Jong-Il Kim and coworkers have reported the in vitro and in vivo correlation of disintegration and bitter taste masking using orally disintegrating tablet containing ion exchange resin – drug complex. Although the taste-masking of bitter drug using ion exchange resin has been recognized, in vitro testing using an electronic tongue (e-Tongue) and in vivo bitterness test by human panel test was not fully understood. In case of orally disintegrating tablet (ODT) containing bitter medicine, in vitro and in vivo disintegration is also importance for dosage performance. Donepezil hydrochloride was chosen as a model drug due to its bitterness and requires rapid disintegration for the preparation of ODT. In this study, ion exchange resin drug complex (IRDC) at three different ratios (1:2, 1:1, 2:1) was prepared using a spray-drying method and then IRDC loaded ODT containing superdisintegrants (crispovidone, croscarmellosesodium and sodium starch glycolate) were prepared by the direct compression method. The physical properties and morphologies were then characterized by scanning electron microscopy (SEM), X-ray powder diffraction (PXRD) and electrophoretic laser scattering (ELS), respectively. The in vitro taste-masking efficiency was measured with an electronic tongue (e-Tongue). In vivo bitterness scale was also evaluated by human volunteers and then we defined new term, “bitterness index (BI)” to link in vitro e-Tongue. There was a good correlation of IRDC between in vitro e-Tongue values and in vivo BI. Further-more, IRDC-loaded ODT showed good in vitro/in vivo correlation in the disintegration time. The optimal IRDC-loaded ODTs displayed similar drug release profiles to the reference tablet (Aricept®ODT) in release media of pH 1.2, pH 4.0, pH 6.8 and distilled water but had significantly better palatability in vivo taste-masking evaluation. The current IRDC-loaded
ODT according to the *in vitro* and *in vivo* correlation of disintegration and bitter taste masking could provide platforms in ODT dosage formulations of donepezil hydrochloride for improved patient compliances.