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In vitro in vivo Correlation of Oral Drug Formulations: An Overview

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Dissolution test is an important quality control tool, provided it is based on a meaningful *in vitro in vivo* correlation (IVIVC). Such dissolution test can prove as a surrogate to the extensive, expensive and time consuming *in vivo* bioavailability testing on humans. This review discusses what are the IVIVCs and different levels of IVIVCs, and encompasses various approaches to seek meaningful IVIVCs, mainly for oral solid dosage forms. Discussed are different modifications in *in vitro* dissolution testing to simulate the *in vivo* environment, to which the formulation is subjected to after oral administration. IVIVCs with high quality and predictability can substantiate such *in vitro* dissolution tests, especially, to guide development of new modified release formulations of drugs with narrow therapeutic window. It also assesses the lot-to-lot quality of the drug product to ensure product safety and efficacy.

Drug absorption after oral administration of a solid dosage form depends on the release of the drug from a formulation, solubilization or dissolution of the drug under the physiological conditions of the gastrointestinal tract (GI tract) and permeation across the GI tract. As first two of these steps are very critical or rate determining, *in vitro* dissolution of a drug is of relevance to predict accurately *in vivo* performance of that formulation. Dissolution test is the only *in vitro* quality control test available till date, which can provide an insight to predict *in vivo* behavior of the drug product. It serves as a tool to distinguish between 'acceptable and unacceptable' (bioequivalent or bioinequivalent) drug products. The value of the dissolution test as a quality control tool is significantly enhanced if an *in vitro in vivo* correlation (IVIVC) is established[1].

Thus dissolution conditions, established on the basis of valid correlation of *in vitro* dissolution with the *in vivo* behavior of the formulation, are used to assess the lot-to-lot quality of the drug product, guide development of new formulations, ensure the continuing product quality and performance.

Dissolution test results depend upon various dissolution test conditions such as pH, volume, ionic strength, deaeration, composition of the dissolution medium, surfactants, agitation intensity and temperature[2,3]. Although dissolution testing is one of the critical assessments to be performed, it can not replace *in vivo* bioavailability testing. Formulation parameters (e.g. drug:polymer ratio, nature of excipients, amount of excipients, type of formulation), dissolution testing factors and physiological parameters decide the dissolution behavior and bioavailability of a drug from the formulation. This may be different for different formulations. Dissolution test results may even vary with the change in the test parameters. So, establishment of proper dissolution standards reflecting *in vivo* performance of a drug is important. Present evidence suggests that, in spite of the fundamental relationship between *in vivo* availability and *in vitro* dissolution rate, no single dissolution test can be applied to all drugs[1].

Often the *in vitro* dissolution test is found to be more sensitive and discriminating than the *in vivo* test. A more

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discriminative dissolution test is preferred from the quality assurance point of view, because it will throw light on possible correlations or changes in the product quality before affecting the *in vivo* performance[4].

Modified release (MR) or Sustained release (SR) or Extended release (ER) formulations are preferred dosage forms for better patient compliance[5] and the dissolution testing for such formulations becomes critical to ensure proper release of the drug. For example, monograph for theophylline ER capsules in USP XXIII[6] and its supplement 9[7], indicate nine different dissolution test conditions for twice-a-day preparations and a separate drug release test for once-a-day preparations with different dissolution limits and insists that the label should claim which type of theophylline release test the present formulation passes.

Further, one has to recognize that testing of each batch for bioavailability on humans is impractical, expensive and time consuming. Therefore, in order to achieve the batch-to-batch bioequivalence, there is a need to correlate the data obtained from bioavailability and bioequivalence studies with *in vitro* quality control procedures (mainly dissolution test)[1].

The concept of *in vitro in vivo* correlation, IVIVC, for ER dosage forms in particular, has been extensively discussed. It continues to be a long sought goal to predict, accurately and precisely, expected bioavailability characteristics for an ER product from its *in vitro* dissolution profile characteristics. This is because the dissolution behavior of the drug from ER or MR dosage forms in the GI tract is the controlling factor for its absorption[4]. It assumes great importance especially for such formulations, which contain drugs having narrow therapeutic window, such as theophylline, diltiazem, carbamazepine, lithium carbonate, nifedipine.

Thus, it is of utmost importance to design a proper *in vitro* dissolution rate test, under well defined test conditions and correlate the data with the bioavailability data obtained after carrying out the *in vivo* absorption and bioavailability studies. Once correlated well with the *in vivo* bioavailability data, such a standardized dissolution test will help to predict *in vivo* performance of a formulation and therefore, can serve as a validated quality control check to assure batch-to-batch consistency of formulations with respect to their physiological performance. Such a validated dissolution test can minimize the use of extensive, expensive and time consuming bioequivalence studies involving humans as the subjects. A dissolution test should also indicate the dissolution stability and hence continued physiological performance of the formulation.

What is *in vitro in vivo* correlation (IVIVC)?

It is a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form, usually the rate or extent of drug dissolution or release, and a relevant *in vivo* response e.g. plasma drug concentration or amount of drug absorbed[4]. To obtain an IVIVC, at least three batches of the same drug should be available which differ in their *in vivo* as well as *in vitro* performance. In case of difference in *in vivo* performance of these batches, *in vitro* test conditions can be suitably modified in order to correlate with the *in vivo* data of the batches. On the other hand, if the *in vitro* behavior is different, it may be possible to modify test conditions to achieve similar dissolution profiles of the batches showing similar *in vivo* behavior, to establish an *in vitro in vivo* correlation[4].

Current Status of IVIVC:

The performance of ER/SR/MR formulations as observed in *in vitro* test does not necessarily mean that those formulations will behave similarly *in vivo*[8]. For example, three different ER diclofenac sodium tablet formulations showed identical *in vitro* dissolution profiles when tested in simulated intestinal fluid (without enzymes), but they exhibited different plasma drug levels when tested in humans[9]. *In vitro* studies of ER solid dosage form prepared from cholesterol for delivering a model antigen indicated that about 20% of the antigen was released within 8 h with a further release up to 15 days[10]. But the same formulation could release about 60% of the antigen in 2 days when tested in mice[11]. Tandt *et al.*[12], have demonstrated that the dissolution test conditions for indomethacin ER formulations (USP Apparatus 1, pH 6.2) failed to discriminate a commercial product from the test product. The *in vitro* dissolution profiles were found to be similar but the test formulation showed longer lag time, lower C_{max} and delayed T_{max} indicating lesser absorption than the commercial indomethacin ER product. In contrast, some reports also indicate good bioavailability of the formulations having poor *in vitro* dissolution profiles. Al-Angary *et al.*[13], have reported that two commercial brands of theophylline ER formulations with significantly different dissolution profiles

in simulated gastric fluid (1 h) followed by simulated intestinal fluid (11 h) (both without enzymes) were bioequivalent when tested in humans. Attempts have also been made to check predictability of disintegration time and dissolution parameters for bioavailability of some conventional tablets of naproxen. Razdan and Nagaraja have reported that these *in vitro* parameters failed to give true indication of bioavailability, when correlated with *in vivo* parameters like AUC and C_{max}[14].

A partial list of the drugs and their formulations, which have been studied for IVIVC, is given in Table 1.

Till 1987 there were no consistently meaningful IVIVCs established for the ER dosage forms[4,15]. In 1988, a USP Pharmacopoeial Forum stimuli article classified the IVIVCs into Levels A, B and C, based on their order of usefulness and the method used to correlate the data, which have been adopted by USP XXIII[4]. A workshop on *In vitro in vivo* testing and correlation for oral controlled/ modified release dosage forms (1990), Washington DC, came up with a concept that development of an IVIVC should be on product by product basis[16]. Various procedures for development, evaluation and application of an IVIVC were described and a concept of validation of dissolution specifications by bioequivalence study involving two batches of the product with dissolution profiles at the upper and lower dissolution specifications was suggested[16]. Levels of correlation are described in detail in USP XXIII, NF XVIII 1995 and also the methods for the establishment of the dissolution specifications[6].

In 1993, during a USP/AAPS/FDA - sponsored workshop on scale-up of oral extended release dosage forms it was identified that the objectives of an IVIVC are to utilize dissolution as a surrogate for bioequivalence testing and to help establish dissolution specifications[17].

Thus, there is an increasing confidence in IVIVC for estimating the *in vivo* bioavailability characteristics of an ER drug product. But, development of an IVIVC with high predictability and identification of specific applications for such correlations is not still well defined. A survey carried out by US FDA Centre for Drug Evaluation and Research, indicates increase in number of times the IVIVCs were developed for the new drug applications (NDA) submission from 9 IVIVCs in 60 submissions (1982-1992) to 9 IVIVCs in 12 submissions (Oct. 1994 - Oct. 1995)[4].

The Schedule Y of the Indian Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rule, 1945, describes 'the Indian Regulatory requirement and guidelines on clinical trials for import and manufacture of New Drug'[18]. It includes bioavailability studies and dissolution studies on oral dosage forms under the category of special studies. These are required to be submitted on the formulations manufactured in the country. The manufacturer has to submit the bioavailability study details and the methodology and other details regarding the comparative *in vitro* dissolution studies for the test and the reference formulations (In-house dissolution method details for the formulations which are not official including dissolution medium, volume, dissolution apparatus, agitation intensity, sampling time/s, temperature and the method of analysis). Although the manufacturer has to submit the performance equivalence reports, separately for *in vivo* performance and for *in vitro* performance, it is not mandatory to establish correlation between the data generated by the *in vivo* testing and the *in vitro* testing of the formulations[18]. On the other hand, establishment of IVIVC and submitting it along with the bioavailability and dissolution study data may help for the waiver in case of post manufacturing changes as per the US FDA guidance[4].

IVIVCs are expected more generally for ER formulations than with IR (immediate release) products, especially when the latter released the drug rapidly ($\geq$ 80% in $\leq$ 20 min)[19]. Recognizing that drug dissolution and GI permeability are the fundamental parameters controlling rate and extent of drug absorption (bioavailability), Amidon, Shah and co-workers, have proposed a biopharmaceutic drug classification scheme for correlation of *in vitro* drug product dissolution and *in vivo* bioavailability[20]. These biopharmaceutic drug classes and the IVIVC expectations for immediate release products are summarized in Table 2.

Thus, *in vitro* dissolution data can be utilized for prediction of *in vivo* performance of the dosage form if there exists a meaningful method for transformation of data. *In vitro* data can not be directly compared with *in vivo* data since measurement of *in vivo* release/ absorption is not straightforward. Even use of classical single point pharmacokinetic parameters such as C_{max} and T_{max} to assess bioavailability/bioequivalence of ER dosage forms is controversial[21]. Various mathematical models and equations have been described in literature for conversion of directly measurable pharmacokinetic

TABLE 1: LIST OF DRUGS AND THEIR FORMULATIONS STUDIED FOR *IN VITRO IN VIVO* CORRELATION

Drug	Dosage form	Reference
Acetaminophen (Paracetamol)	Tablets, Multiple unit capsules	3, 68
Aminorex	Sustained release	69
Aminosalysilic acid	Tablets	70
Ampicillin	Capsules	71
Aspirin	Tablets, Coated tablets, Capsules, Timed release tablets	72-76, 77
Bacampicillin	Microcapsules	78
Bromocryptine	Modified release capsules	40
Cephalexin	SR tablets	79
Chloramphenicol	Tablets	80
Chlorothiazide	Tablets	81
Chlorpromazine	Tablets	82
Cinoxacin	Capsules	83
Diazepam	Uncoated tablets	84
Diclofenac sodium	CR matrix tablets	85
Dicumarol	Tablets	86
Diethylcarbamazine	SR tablets	87
Digoxin	Tablets	88-93, 94, 95
Diltiazem.HCl	SR formulations	59
Doxantrazole	Tablet, Suspension	96
Doxycycline	Capsules	97
Erythromycin stearate	Tablets	98
Flufenamic acid	Capsules	99
Furosemide	Tablets	100
Griseofulvin	Tablets,	101
	Tablets, Capsules	102
Hydrochlorothiazide	Tablets	103
Ibuprofen	Modified release capsules	34, 104
Iloprost	SR capsules	105
Indomethacin	Microcapsules	106
Lithium carbonate	Tablets, Capsules	107
Mefenamic acid	Capsules	108
Methaqualone	Tablets, Solid dosage forms	109, 110

Drug	Dosage form	Reference
Methenamine	Tablets	81
Nalidixic acid	Uncoated tablets	111
Nitrofurantoin	Tablets, Capsule, Solid dispersions	81,112, 113, 114
Papaverine	Tablets	115
Phendimetrazine	SR products	116
Phenobarbitol	Tablets	117
Phenylbutazone	Tablets	118
Phenytoin	Tablets	115
Phenytoin sodium	Capsules	119
Prednisone	Tablets	120, 121, 122
Propranolol.HCl	Immediate release and Extended release formulations	41
Pseudoephedrine sulphate	SR tablets	123
Pseudoephedrine.HCl	CR tablets	44
Quinidine	Tablets	124
Quinine.HCl	Enteric coated tablets	125
Remoxipride	SR coated spheres	2
Riboflavine	Sugar coated tablets	126
	SR formulation	127
Salbutamol sulphate	Immediate release, Osmotic pump	128
Sodium-p-aminosalicylate	Enteric coated tablet	125
Sodium sulphanilate	Enteric coated tablet	125
Spironolactone	Tablets	129
Sulfamethazine	Tablets	130
Sulfamethoxazole/Trimethoprim	Tablets	131
Sulfisoxazole	Tablets	115
TA-5707F	CR tablets	45
Tetracycline and Oxytetracycline	Oral preparations	132
Theophylline	SR tablets, ER tablets	58, 133
	SR formulations, Oral formulations	134, 135
	Diffusion controlled DDS	136
	Microspheres	137
Tiopinac	Solutions and capsules	138
Triple Sulfa	Tablet, Suspension	139, 140
Warfarin	Tablets	141
Zidovudine	Microspheres	142

data to release/absorption characteristic of drug from the dosage form for comparison with *in vitro* data e.g. Wagner-Nelson model[22], Moment analysis[23] and Deconvolution [24-26].

Levels of correlation:

US FDA guidance to industries on extended release oral dosage formulations gives good account of different levels of correlation[4] -

Level A correlation is the highest category of correlation. It is a point-to-point relationship between the *in vitro* data and the *in vivo* data. The data treatment involves Wagner-Nelson method or Loo-Reigleman method or deconvolution followed by comparison of fraction of the drug absorbed and the fraction of drug dissolved *in vitro* to obtain a linear correlation. The dissolution conditions in such a case can serve as surrogate for *in vivo* performance of the formulation and no additional human studies are needed to justify change in manufacturing site, raw material supplier or minor formulation changes. It can act as a meaningful quality control procedure predictive of the *in vivo* performance of the formulation.

In case of **Level B** correlation, mean *in vitro* dissolution time ($MDT_{in\ vitro}$) is compared with mean *in vivo* residence time (MRT) or mean *in vivo* dissolution time ($MDT_{in\ vivo}$). Thus, although all the data obtained from *in vitro* and *in vivo* studies is utilized for establishing correlation, there is no point-to-point relationship. The data treatment involves statistical moments analysis. This type of correlation does not uniquely reflect actual *in vivo* behavior of the formulation, because a number of different *in vivo* profiles will produce similar MRT values. This has a very limited use in formulation development.

Level C correlation involves a single point relationship between dissolution test data and bioavailability of the drug (e.g. $t_{50\%}$ *in vitro* or % drug dissolved in 4 h and AUC/C_{max}/t_{max}). It does not utilize all the data and hence, cannot reflect the complete plasma concentration-time curve. Thus, it can only serve as guide in formulation development or as a production quality control procedure.

Multiple level C correlation relates more than one pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile. Indirectly, if a Multiple level C correlation exists there is a possibility of Level A correlation. Therefore, in such cases Level A correlation is to be sought.

Approaches to seek correlation between *in vitro* dissolution data and *in vivo* performance of the formulation:

Various approaches have been adopted to establish the *in vitro-in vivo* correlation. The use of various mathematical[27-30], statistical models[3,30-33], optimization

TABLE 2 : BIOPHARMACEUTICAL CLASSIFICATION OF DRUGS

Class	Solubility	Permeability	IVIVC expectations
I	High	High	IVIVC- if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlation
II	Low	High	IVIVC- expected if *in vitro* dissolution rate is similar to *in vivo* dissolution rate, unless dose is very high
III	High	Low	Absorption (permeability) is rate determining and limited or no correlation with dissolution rate
IV	Low	Low	Limited or no IVIVC expected

Note: Here a limited correlation means that the dissolution rate while not rate controlling may be similar to the absorption rate and the extent of correlation will depend on the relative rates. (Ref. # 20)

techniques[34] as well as computer softwares[29,31,35-39] has been reported. Different methods for evaluating and correlating *in vitro* dissolution parameters with some *in vivo* parameters have been published. Drewe and Guitard[40] have applied various methods to establish *in vitro in vivo* correlation for different bromocryptine MR capsules, which are as follows:

a. Comparison of cumulative absorption profile and cumulative *in vitro* dissolution profile.

b. Correlation of corresponding times to dissolve and respectively, absorb 'the same fraction of the dose (for approximately 80-100 % of the dose).

c. Correlation between first order dissolution rates and respective bioavailability data by plotting *in vitro* dissolution rate constants v/s relative AUC (good linear correlation, r = 0.994).

d. Correlation of cumulative percent dissolved v/s $(time)^{-2}$.

e. Correlation between *in vitro* mean dissolution time and *in vivo* mean dissolution time (weak linear correlation, r = 0.91).

Rekhi and Jambhekar[41] calculated fraction of drug absorbed at a given time for propranolol hydrochloride extended release bead products and correlated it with fraction of drug released *in vitro* at the corresponding times. Liu, *et al.*[42] have proposed a method for analysis of the IVIVC of ER formulations. This method utilizes incremental values of dissolved or absorbed fractions of the drug, instead of the cumulative fractions released or absorbed, to construct a x^2 for demonstrating the *in vitro in vivo* similarity of an ER product. These x^2 s enable comparison of different *in vitro* dissolution profiles of a product to come to an appropriate dissolution profile representing the *in vivo* release pattern of the product.

USP-XXIII (1995)[6] gives different levels of correlation (level A, B and C)[43] which utilize various mathematical and statistical techniques for establishment of *in vitro in vivo* correlation such as convolution and deconvolution method, statistical moment analysis and single point comparison method. US FDA guidance to industries on extended release oral solid dosage forms[4] indicates multiple level C correlation along with the correlation levels described in USP XXIII.

The most commonly used methods include comparison of fraction absorbed *in vivo* and fraction released *in vitro* at given times (Wagner-Nelson method/ deconvolution method)[2,3,25,44] and statistical moment analysis[45].

Statistical moment approach (mean time parameters) can facilitate correlation between *in vitro* dissolution parameter and bioavailability parameter and in turn, help to predict bioavailability of the formulation by monitoring its dissolution profile[46,47].

Brazzell and Kaplan[46] have appreciated the potential of statistical moments analysis for the determination of model independent estimates of *in vivo* dissolution and absorption rates and have studied various factors which affect the accuracy of mean absorption times (MAT) and mean dissolution times (MDT), thus, estimated. Simulation techniques were used to assess the ability of statistical moment analysis to provide accurate estimates of absorption and dissolution rates and the effects of sampling schedule, random error and the estimate of the terminal elimination rate constant on the accuracy of these estimates. Simulated drug concentration - time data were generated for intravenous bolus, oral solution and tablet dosage form using two-compartment model and evaluated four different sampling schedules. Determination of mean time parameters with normally distributed random error (CV, ± 10%) and for four different sampling schedules indicated that sample schedule is critical for obtaining accurate and meaningful estimates of MATs and MDTs. Thus, accuracy of the results and meaningful conclusions using statistical moment analysis are dependent on the design of the study from which the data is generated. Thus, expansion of sampling schedule to longer times can help to minimize the impact of error in the determination of elimination rate constant inherent due to biological and analytical variability. Finally the optimum information, in terms of estimates of MATs and MDTs, can be generated using frequent sampling during absorption phase and adequate sampling during the terminal elimination phase to minimize impact of extrapolation error on the estimate of elimination rate constant.

Block and Banakar[47] have demonstrated the utility and inherent simplicity of this model independent approach to IVIVC by transforming the data possessing poor correlation between *in vitro* and *in vivo* parameters. They have applied Mean Time concept based on statistical moments for IVIVC to the *in vitro* and *in vivo* data generated by McNamara *et al.*, for six furosemide

TABLE 3 : MEAN TIME PARAMETERS USING STATISTICAL MOMENTS

Factor	Furosemide tablet formulation			Correlation coefficient
	A	C	D	(p<0.05)
$MRT_{in\ vivo}$ (urinary excretion data)	0.74	1.18	1.12	0.99[a]
$MRT_{in\ vitro}$ (dissolution data)	1.26	1.34	1.33	0.98[b]
$MRT_{in\ vivo}$ (plasma data)	10.72	11.46	11.20	

[a] correlation coefficient between $MRT_{in\ vivo}$ using urinary excretion data and $MRT_{in\ vitro}$

[b] correlation coefficient between $MRT_{in\ vivo}$ using plasma concentration - time data and $MRT_{in\ vitro}$ (Ref. # 47)

tablet formulations using both plasma concentration-time data and urinary excretion data. There was satisfactory improvement in the correlation between $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$ after transformation of the data using statistical moments with correlation coefficient 0.99 and 0.98 at $p<0.05$ when urinary excretion data and plasma concentration data was used, respectively. The details are shown in the Table 3.

Typical plots indicating different approaches to establish an IVIVC model (Level A, B and C) are indicated in Fig. 1[48], 2 and 3.

Determination of correlation and related calculations:

The data obtained from the *in vivo* studies (plasma concentration v/s time data) is used to calculate the amount of drug absorbed into systemic circulation using either Wagner-Nelson method[20,30,44] (which considers body as a single compartment) or mathematical deconvolution method[4,22,23] (which needs plasma concentration - time data for a fast releasing formulation i.e. intravenous (i.v.)/ fast-release oral formulation like solution or suspension or tablet for comparison). These methods utilize all the *in vivo* and *in vitro* data available, which is essential for development of Level A correlation. For Level B correlation, some mean parameters like MRT or $MDT_{in\ vivo}$ and $MDT_{in\ vitro}$ are compared[1,21]. Although all the *in vivo* and *in vitro* data is being used in this kind of correlation, it can not be a point to point correlation. And in case of level C correlation, particular *in vivo* parameter ($C_{max}/T_{max}/AUC/T_{1/2}$) for formulations with different *in vitro*

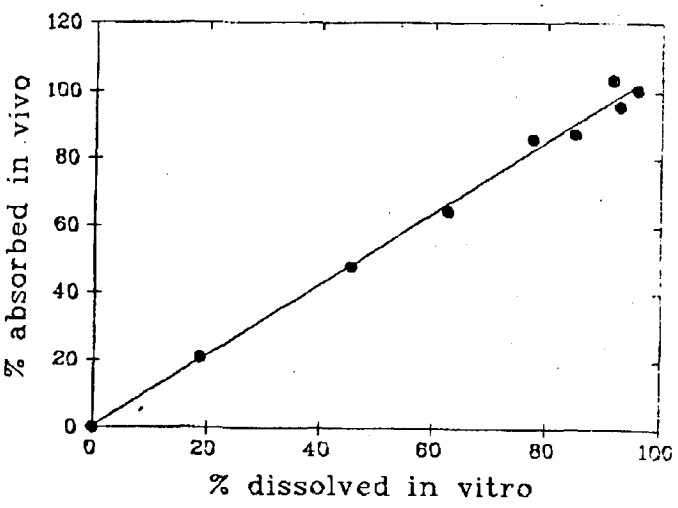

Fig. 1 : Level A *in vitro in vivo* correlation [48]

Correlation between % theophylline dissolved *in vitro* (dissolution medium - simulated gastric fluid without enzyme followed by pH 6 phosphate buffer) and % theophylline absorbed after administration of theophylline extended release formulation (microspheres filled in hard gelatin capsule) to healthy human volunteers calculated by using Wagner-Nelson method

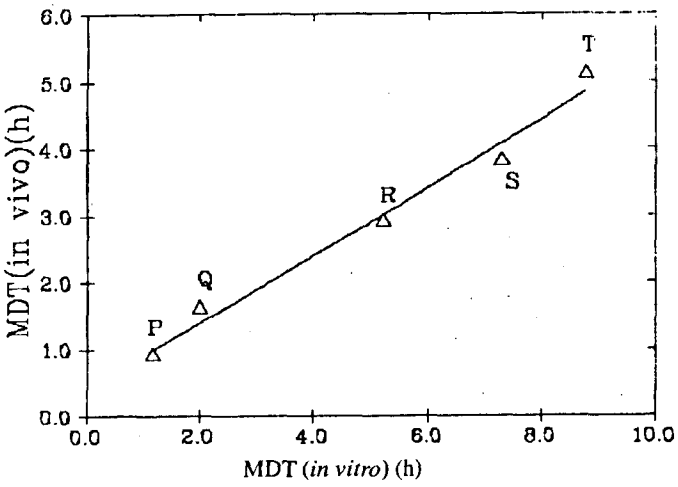

Fig. 2 : Level B *in vitro-in vivo* correlation

Schematic representation of correlation of mean *in vitro* dissolution time (h) ($MDT_{in\ vitro}$) with mean *in vivo* dissolution time ($MDT_{in\ vivo}$) for five formulations, P, Q, R, S and T showing different *in vitro* dissolution behavior under given dissolution conditions

dissolution behavior are correlated with specific *in vitro* dissolution parameter (T_{90}/T_{50}/per cent dissolved in 45 min) and equation for the correlation is established[1,4,49].

Cumulative relative fraction absorbed (CRFA) can be calculated by using the Wagner-Nelson method from the following equation and correlated to the cumulative fraction dissolved *in vitro*[4,22,44]

$$CRFA = (C_t + K_{el} \cdot AUC_{0-t})/(K_{el} \cdot AUC_{0-\infty}) \quad \ldots\ldots 1$$

where C_t is the plasma drug concentration at time t, K_{el} is the elimination rate constant, AUC_{0-t} is the area under the curve from time zero to time t and $AUC_{0-\infty}$ is the area under the curve from time zero to time infinity.

Convolution method[4] predicts plasma drug concentrations using a mathematical model based on the convolution integral as given in the following equation,

$$C_t = \int_0^t C_\delta\,(t\text{-}u)\, r_{abs}\,(u)\, du \quad \ldots\ldots 2$$

where, C_t is the plasma drug concentration resulting from the absorption rate constant (r_{abs}), C_δ is the concentration time course that would result from the instantaneous absorption of a unit amount of drug and can be estimated from either i.v. bolus data, oral solution, suspension or rapidly releasing (*in vivo*) dosage forms.

Deconvolution method[4,24] estimates the time course of drug input (usually *in vivo* absorption or dissolution) using a mathematical model based on the same convolution integral as given in equation 2.

Mean residence time (MRT)[1,4,23] (or mean transit time) is the mean time for which the drug resides in the body and is calculated by using the equation:

$$MRT = AUMC/\ AUC \quad \ldots\ldots 3$$

where AUC is the area under the plasma concentration time curve and AUMC is the area under the moment curve.

Mean absorption time (MAT) is the mean time required for the drug to reach the systemic circulation from the time of drug administration and is calculated as

$$MAT = MRT_{oral} - MRT_{i.v.} \quad \ldots\ldots 4$$

Mean *in vitro* dissolution time ($MDT_{in\ vitro}$) indicates the mean time for the drug to dissolve under *in vitro* dissolution conditions and is determined using the following equation,

$$MDT_{in\ vitro} = \{\int_0^\infty (M_\infty - (t))\, dt\}/\ M_\infty \quad \ldots\ldots 5$$

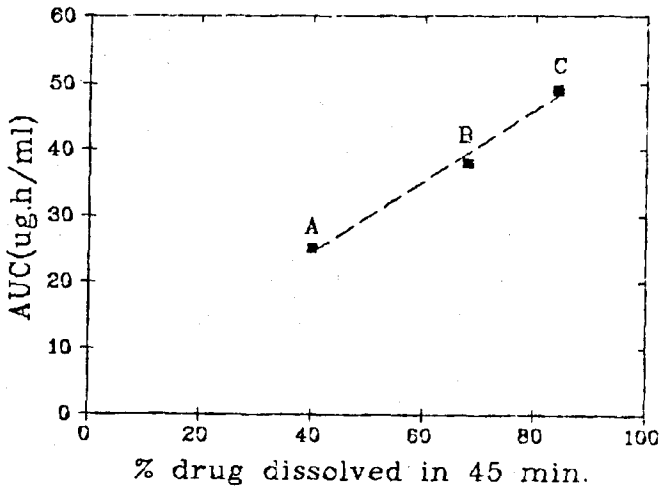

Fig. 3 : Level C *in vitro in vivo* correlation

Schematic representation of correlation between % drug dissolved in 45 min. (*in vitro* dissolution parameter) and AUC (area under the plasma concentration - time curve) obtained from the plasma concentration (µg/ml) v/s time (h) curve for three formulations, A, B, C, showing slow, medium and fast *in vitro* dissolution, respectively, under given dissolution conditions

Finally, mean *in vivo* dissolution time reflects mean time for drug to dissolve *in vivo* and is calculated using the equation,

$$MDT_{solid} = MRT_{solid} - MRT_{solution} \quad \ldots\ldots\ldots\ldots 6$$

i.e. $$MDT_{in\ vivo} = MRT_{solid} - MRT_{solution}$$

Makoid, Banakar and Dufoure have reviewed several approaches for modeling of dissolution profiles (*in vitro* as well as *in vivo*) of controlled release systems[50]. As the success of any drug delivery system is governed by the drug absorption performance which is a function of the drug release, assuming relatively fast absorption following drug dissolution, it is important to select proper model for assessing the dissolution behavior and hence the *in vivo* performance of that particular formulation. They have explored several mathematical models and the parameters obtained after fitting them to the same data set. The models were assessed in terms of the statistical parameters - sum of squared deviations, r-squared, coefficient of determination, correlation and model selection criterion. The model with lowest (approaching to zero) value for sum of squared deviations, values > 0.99 for r-squared, coefficient of determination and correlation and highest possible value for the model selection criterion indicate the best fitting model. For modeling desired release profile from a controlled release formulation Makoid, *et al.*, have suggested Makoid function which considers a zero order process being shut down, or followed, by a first order process and the cumulative amount released is given as

F = (1-FL)*FE+FL*FM ..... Makoid function

where, FL = UNIT(T/1-C)

FE = B*T*EXP((-C)*T)

FM = B/C*0.36788

Here, time (T) is the independent variable and the cumulative amount (or fraction) released (F) is the dependent variable and A, B, and C are the parameters studied; A = Time shift (A = positive, the data has a lag time, A = negative, the data has burst effect), B = zero order release rate and C = first order shut down rate.

Similarly, corrected time, T = (TIME-A)*UNIT (TIME-A), where TIME is the real time.

However, this function could not take care of the gradual early release of the drug from the formulation. Hence they modified this function to accommodate the gradual early drug release to get sigmoid shaped release profile. The modified Makoid function considers the same independent and dependent variables and parameters and the equation is given as,

F = FL3*(FE*FL1+FL*(1-FL1))+(1-FL3)*FM

..... Modified Makoid function

where,

FL3 = UNIT(-T3); FL1 = UNIT(-T1);

FM = B/C*EXP(C/A-C/B-1); FL = B*T2*EXP((-C)*T1); FE = EXP(A*TIME)-1;

T1 = TIME-TS; T2 = TIME-TL; T3 = TIME-TM;

TS = LN(B/A)/A; TL = TS-1/A+1/B; TM = 1/C+TL

The modified Makoid function has resulted in improved statistical parameters ensuring better fit of the model to the drug release data. It has been pointed out that although several model equations might be useful in the evaluation of the dissolution as well as absorption profiles, the least complicated model, which reflects the data to the level necessary for predictions should be selected[50].

Simulation of *in vivo* environment (to which the formulation is subjected after administration) in the *in vitro* dissolution test:

In case of oral solid modified release dosage forms specific dissolution conditions are established after studying thoroughly the environment in the gastrointestinal tract to which the formulation is subjected and attempts are, thus, made to simulate these conditions as close as possible[51]. Khan has reviewed several approaches to simulate the *in vivo* environment in the *in vitro* dissolution[8].

Aoki *et al.*[52], have modified the paddle method by inserting the polystyrene beads to simulate the GI motility and mucin plugs after administration of phenylpropylamine hydrochloride matrix tablets into fasted beagle dogs. They observed that the modified paddle method showed better IVIVC as compared to the conventional paddle method.

El-Arini *et al.*[53], attempted to simulate the pH of the GI tract and the food induced changes to the bioavailability of theophylline from beads either embedded in the tablet or filled in the capsule. They inserted a dialysis cell containing the dosage form in a small volume of fluid in the dissolution medium in a dissolution vessel and the

physiological conditions were simulated by adjusting the fluid of dialysis cell. This has enabled the testing of ER formulations under various food induced conditions.

Macheras *et al.*[54], have used milk with various levels of fat content as the dissolution medium and demonstrated direct relationship between fat contents of milk and the dissolution data for theophylline matrix tablet or capsule formulations. They could achieve good correlation between *in vivo* data obtained after administration of these formulations in humans after a high fat meal and the dissolution data obtained using 7.5% fat content milk as the dissolution medium.

The effect of addition of different solubilizers into the dissolution medium on *in vitro* dissolution of drug having poor aqueous solubility has been studied by Abrahamsson *et al.*[55]. They have demonstrated that addition of solubilizer in the dissolution medium provided the data with a good IVIVC for felodipine matrix tablet formulations but have cautioned that choice of solubilizer affects the results.

The dissolution test conditions have been modified by adding solubilizer in the dissolution medium and a stationary basket to hold the dosage form above the paddle to achieve reproducible hydrodynamic conditions for felodipine (a model drug having poor water solubility) matrix tablet formulation. This resulted into the dissolution data with a good IVIVC and this method was capable to discriminate the formulations with different *in vivo* performance[56].

Maturu *et al.*[57], have simulated the effect of high fatty food on the *in vivo* behavior of theophylline matrix tablets and beads filled in capsules by treating the dosage form (or contents) in peanut oil for 2 h prior to standard dissolution testing. The dissolution data, thus obtained, showed good correlation with *in vivo* percent dissolved in humans after high fat breakfast.

Rekhi and Jambhekar[41] have found that change-over dissolution medium (simulated gastric fluid for 1 h and simulated intestinal fluid for 11 h) gave better IVIVC than the data obtained using distilled water as the dissolution medium for propranolol hydrochloride ER bead products prepared using aqueous polymeric dispersions.

Tandt *et al.*[58], studied dissolution of marketed theophylline ER formulations (Theodur® and Retafyllin) at different pH conditions (pH 3, 4, 5, 6, 6.8 and 7.5). They simulated the *in vivo* performance of these formulations using biorelevant technique. It was observed that simulated profiles obtained from dissolution data using pH 6.0 buffer were superimposible with the actual *in vivo* profiles of Theodur® but for Retafyllin, the data obtained using pH 4.0 buffer as the dissolution medium served the purpose well.

In recent times, much effort has gone into establishing the IVIVCs for different types of MR formulations and utilize them for the development of optimum formulation[59]. Various attempts are being made to establish the correlation either by developing discriminating *in vitro* dissolution tests[60-62], biorelevant dissolution test conditions[58] or identifying the biorelevant dissolution conditions by systematic study of different physicochemical properties of the *in vivo* environment and trying to simulate those, *in vitro*, followed by comparison of the *in vitro* release profiles with the *in vivo* absorption profiles[2,3]. Some workers have utilized well-established pharmacokinetic parameters and the *in vitro* dissolution study data to predict the *in vivo* behavior of the formulation[58]. Simulation of GI tract conditions may help to understand the fate of the drug administered in a particular dosage form by oral route beforehand and thus, help to develop the optimum formulation. In this regard Abuzarur-Aloul *et al.*[2,3], have thoroughly studied various *in vitro* dissolution test parameters like agitation, temperature, osmolality and polarity of the dissolution medium and their effect on the dissolution of remoxipride from ER-coated spheres to arrive at critical dissolution test conditions which reflect the *in vivo* behavior of the formulations in terms of a level A correlation[2]. They have also investigated the effect of different *in vitro* variables like agitation, pH, osmolality, viscosity and the presence of the bile salts on the dissolution rate of paracetamol from the formulation and established an IVIVC for multiple-unit capsules of paracetamol [3]. They have evaluated the effects using two separate statistical models to predict the optimum *in vitro* dissolution test conditions, which are most closely correlated with the *in vivo* performance of the formulations. Both the models utilize partial least squares analysis. In case of model I, the responses were expressed as cumulative percentage of paracetamol dissolved at specified time points while in model II, the shape and scale parameters according to Weibull function were used as the response. Both the models proved to be good prediction models to develop critical *in vitro* dissolution test conditions and thus, help in establishing IVIVC for oral ER formulations.

Future trends in the field:

Many laboratories are engaged to find better means to estimate *in vivo* behavior of the drug after oral administration by using simple *in vitro* dissolution tests. Efforts are on to modify the dissolution specifications to surrogate the bioavailability and the *in vivo* testing[63]. Several computer programmes have been developed to simulate *in vivo* release pattern of the dosage forms by using the data obtained from the *in vitro* dissolution of the formulations or to help for development of an IVIVC[29,31,35-39]. Various approaches are adopted to achieve better IVIVC (linear models, nonlinear models and other statistical models)[30-33,42,63]. Even for immediate release formulations, in new biopharmaceutical classification of the drugs based on the solubility and permeability of the drugs, the chances to achieve good IVIVCs have been studied thoroughly[20]. Newer concepts, like validation of the IVIVC for its reliability to estimate the *in vivo* behavior of the formulation, have emerged[4,64,65]. Applicability of Artificial Neural Networks (ANNs) towards IVIVC of ER formulations has been tested[30,32,66,67]. ANNs have the potential to be used as reliable predictive tool that may overcome some of the difficulties associated with classical regression methods (especially, difficulty of providing prior specification of the regression equation structure). This may demonstrate higher degree of reliability in the predicted *in vivo* behavior of the formulations[66].

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