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EDITORIAL

Computational pharmacokinetics and *in vitro-in vivo* correlation of anti-diabetic synergistic phyto-composite blend

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Abstract

Despite tremendous strides in modern medicine stringent control over insulin resistance or restoration of normoglycemia has not yet been achieved. With the growth of molecular biology, omics technologies, docking studies, and *in silico* pharmacology, modulators of enzymes and receptors affecting the molecular pathogenesis of the disease are being considered as the latest targets for anti-diabetic therapy. Therapeutic molecular targets are now being developed basing on the up or down regulation of different signaling pathways affecting the disease. Phytosynergistic anti-diabetic therapy is in vogue both with classical and non-classical medicinal systems. However its chemo-profiling, structural and pharmacokinetic validation awaits providing recognition to such formulations for international acceptance. Translational health research with its focus on benchside product development and its sequential transition to patient bedside puts the pharma RDs to a challenge to develop bio-waiver protocols. Pharmacokinetic simulation models and establishment of *in vitro-in vivo* correlation can help to replace *in vivo* bioavailability studies and provide means of quality control for scale up and post approval modification. This

review attempts to bring different shades highlighting phyto-synergy, molecular targeting of antidiabetic agents *via* different signaling pathways and bio-waiver studies under a single umbrella.

Key words: *In silico* pharmacology; Phytosynergistic; Anti-diabetic; Simulation models; Translational health research; Bio-waiver; Signaling pathways

Core tip: The current research scenario on anti-diabetic drug development pipeline focuses on pharmacological targets influencing the molecular pathogenesis of the disease. It encompasses receptors and enzymes that will increase insulin sensitivity, intracellular insulin signaling, enhance peripheral glucose utilizations, suppress hepatic glucose production and reduce circulating triglycerides levels. Combination therapy has gained significance either with herbal or synthetic drugs, though "phytosynergy" awaits proper validation to give rise to new generations of "phytopharmaceuticals". Pharmacokinetic simulation models and established *in vitro-in vivo* correlation that may be extrapolated to humans can serve the purpose of bio-waiver in product transition from lab bench to patient bedside.

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INTRODUCTION

The constant escalations in the number of diabetics worldwide has given an alarming signal and fueled intensified research for the development of new therapeutic entities and latest effective therapeutic regimen. The statistics of the global diabetic population is expected to show a steady growth to 366 million by 2030 of which 90% will be type 2 diabetics. The international diabetes federation has estimated the number of diabetics in India to be 40.9 million, which is expected to grow to 60.9 million by 2025[1-3]. Diabetes is a common metabolic disorder with abnormal elevations in the blood-gluco-lipid profile, leading to major complications like diabetic neuropathy, nephropathy leading to end stage renal disease, retinopathy leading to blindness and diabetic foot ulcers necessitating limb amputations[1,2]. Type 2 diabetes is characterized by the hallmark of insulin resistance and β-cell dysfunction and ultimate destruction of pancreatic insulin secreting cells. Combating insulin resistance with the existing pharmacological approaches are unsatisfactory primarily because although they may compensate for the defects in insulin secretion and action, but are ineffective in counteracting β-cell dysfunction and handling the secondary complications of type 2 diabetes[1-3]. While developing a novel anti-diabetic chemical entity, latest drug design approaches focuses on activation-inhibition of enzymes in insulin-sensitive cells, minimization of associated side effects like obesity, substitution or antagonizing of physiological hormones and their pathways. With the advancements in high throughput screening, proteomics, genomics, molecular docking, and combinatorial chemistry, new therapeutic entities are being developed that influence enzyme activities, signaling receptors and pathophysiological pathways[1,2]. Modern day quantitative structural activity relationship and docking studies are enabling development of bio-active molecules that can achieve structural modifications and thereby alter their pharmacological actions and pharmacokinetic profile so as to maximize bioavailability and minimize the side effects[4-10].

Latest anti-diabetic drug development pipeline focuses on pharmacological targets which include receptors and enzymes that will increase insulin sensitivity, intracellular insulin signaling, enhance peripheral utilizations of glucose, suppress hepatic glucose production and reduce the levels of circulating tri glycerides[4-10].

Medicine in recent times, whether western classical or phyto-therapy, advocates for combination therapy, instead of single approach. Synergy research in phyto-therapy, with the aid of "omics technologies" needs a rationale for establishing its pharmacological and therapeutic superiority to treat diseases which have hitherto been treated using synthetic drugs alone[11-15].

Along with the paradigm of translational health research with the perspectives of bench to bedside approach; all pharmaceutical RDs target to develop robust, cost effective, enhanced throughput *in vitro* assays which may be extrapolated to humans and serve the purpose of bio-waiver. The development of increased number of new chemical entities obviates the need of enhanced pharmacokinetic studies. Though human pharmacokinetic *in vivo* studies are often considered as the "gold standard" for assessment of bioequivalence but it is expensive, time consuming and difficult to handle enormous amount of pharmacokinetic data. Development of pharmacokinetic simulation models which are computational or mathematical tools help to interpret drug kinetics in living environment under specified conditions and can waive off bioequivalence requirements called bio-waiver studies. Establishment of *in vitro-in vivo* correlation (IVIVC) provides a justified explanation for bio-waiver during scale up or post approval changes[16-25].

Thus the editorial encompasses the broad areas highlighting phyto-synergy, targeting of different signaling pathways of type 2 diabetes and how computational pharmacokinetics and development of IVIVC serves the purpose of bio-waiver.

MOLECULAR PATHOGENESIS OF TYPE 2 DIABETES

Treatment regimen of type 2 diabetes advocates two different approaches, one recommending the sequential use of anti-diabetics and another is a pathophysiologic approach which aims to control the disease conditions basing on pathogenesis with a comparative preference on combination therapy.

American Diabetes Association guidelines incorporated an individualized ABCDE anti-diabetic therapy approach where each alphabet refers to A-age, B-body weight, C-complications (micro and macro vascular), D-disease duration and E-life expectancy and expense. Progressive β-cell destruction coupled with the development of insulin resistance in liver, muscles and adipocytes, subsequent elevation in glycated hemoglobin level being the common pathogenic hallmark in all type 2 diabetes mellitus, though variations are reported amongst different ethnic groups[4-6].

Apart from insulin resistance, a host of cardiovascular co-morbidities like dyslipidemia, hypertension, and central visceral adiposity occur in type 2 diabetes. Evidence based contemporary research paradigms have shown that intra abdominal or visceral fat depots synergize defective insulin action and secretion. Moreover leptins, adiponectins, tumor necrosis factor-α, resistin which are secreted from the adipose tissues interfere with glucose metabolism and insulin sensitivity giving rise to the concept of lipotoxicity in type 2 diabetes. These adipokines greatly modify insulin signaling pathways and promote development of insulin resistance. A triadic relation is found to exist amongst β-cell destruction, insulin resistance and adiposity[4-6].

Sedentary lifestyle, westernized dietary pattern, stress, anxiety, depression, smoking and alcohol consumption are other contributing risk factors of type 2 diabetes. Obesity is also found to be associated with endothelial dysfunction, impairs muscle microcirculation, retards entry of insulin and blood glucose into skeletal muscle and decreases their availability to muscle cells. Lack of physical activity is an important risk factor in type 2 diabetes. Daily physical activities decreases visceral and body fat, increase glycogen synthase (GS) content of the muscle, promotes non-oxidative disposal of glucose as glycogen and activates glucose transporter subtype 4 (GLUT4) to enhance peripheral glucose utilization. Physical activity up regulates expression and activity of proteins involved in insulin signal transduction, improves oxidative capacity of the skeletal muscles, decreases free fatty acid concentrations and enhances the increased expression of downstream signaling components of insulin. Regular exercises also trigger the release of anti-inflammatory cytokines, a protective role against insulin resistance[1,4-6].

An insight into the genetics of type 2 diabetes showed that genes encoding proteins are involved in insulin signaling, glycogen synthesis and glucose transportation, fatty acid uptake and synthesis, adipocyte differentiation and thus suggests associations with diabetes. A clear understanding of human genome sequence is necessary which will help in rapid identification of the genes associated with diabetes. Mutations of five genes viz. glucose metabolizing enzyme glucokinase, transcription factors hepatocyte nuclear factor (HNF) 1α and β, HNF4α and insulin promoter factor 1 (IPF1) affect moderate to significant reductions in insulin secretions. Latest research reporting does have mentioned that genetic variation of newly encoded gene Calpain, called as *CAPN10* gene can cause diabetes[5-9].

THERAPEUTIC MOLECULAR TARGETS BASED ON RECEPTOR SIGNALING PATHWAYS IN TYPE 2 DIABETES

Amongst the Oral Hypoglycemic Agents (OHAs) mostly recommended for type 2 anti-diabetic therapy, sulfonylureas (*e.g.*, tolbutamide, glibenclamide, acetohexamide) and biguanides (*e.g.*, phenformin, metformin) are in wide use followed by thiazolidinediones (also known as glitazones, *e.g.*, Rosiglitazone, Pioglitazone) and alpha glucosidase inhibitors (acarbose, miglitol, voglibose). Sulphonyl ureas work primarily by stimulating pancreatic insulin secretion and reduce the hepatic glucose output and enhance peripheral glucose utilizations. Biguanides are anti-hyperglycemic agents rather than hypoglycemics, suppress excessive hepatic glucose production, increases peripheral glucose utilizations to a lesser extent, reduce intestinal glucose absorption by reducing food intake. Alpha glucosidase inhibitors delay the breakdown of disaccharides and polysaccharides and hence glucose absorption is delayed. Thiazolidinediones enhance insulin sensitivity in peripheral tissues.

However, the available pharmacological approaches for anti-diabetic therapy are not successful enough to put a stringent control on insulin resistance. Instead of mono therapy now combination therapy and muti-drug formulations are in vogue. With the development of proteomics, genomics and a thorough understanding of the molecular pathways, the development of new molecular targets with anti-diabetic potentials focuses in modulating pharmacokinetics, cellular location, overall distribution etc. Modulators of enzymes and receptors are now becoming the molecular targets for any disease therapy[8-10].

The three targeted tissues of insulin action include skeletal muscle, adipose tissue and liver. Insulin binds with the target cell surface receptor and activates the tyrosine kinase which is a constituent of the receptor molecule. Tyrosine residues of the insulin receptors undergo autophosphorylation and the serine/threonine residues become phosphorylated[7-10]. In type 2 diabetes elevated levels of insulin stimulates serine kinases *via* IGF-1 receptor (Insulin like growth factor 1) leading to insulin resistance[7-10]. Protein kinase C (PKC) is known to play a significant role in developing

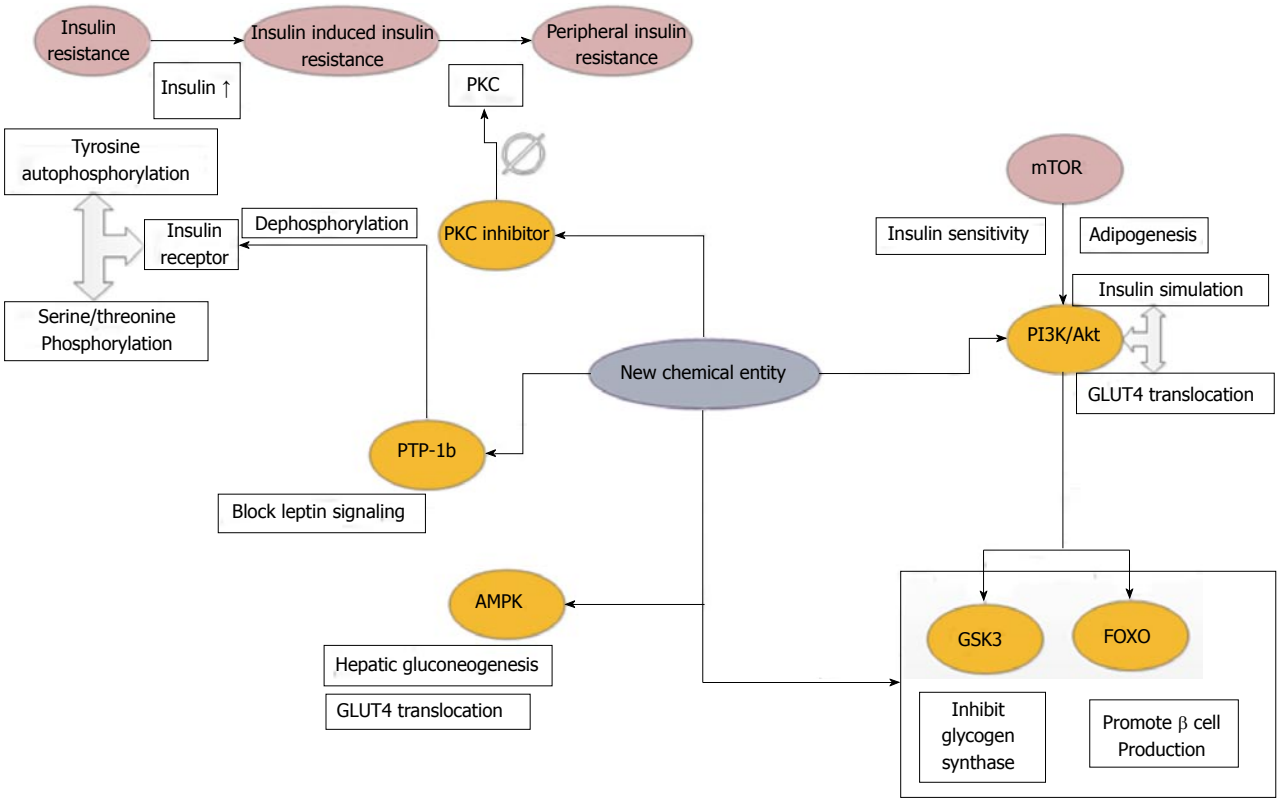

Figure 1 Schematic representation of different receptor signaling pathways in type 2 diabetes mellitus which can be targeted by new chemical entity. PKC: Protein kinase C; Akt: Also known as protein kinase B (PKB); GSK3: Glycogen synthase kinase 3; mTOR: Mammalian target of rapamycin; FOXO: Forkhead box subgroup O; PTP-1b: Protein tyrosine phosphatase-1b; GLUT4: Glucose transporter Subtype 4; PI3K: Phosphoinositide 3 kinase; AMPK: AMP activated protein kinase.

peripheral insulin resistance. Thus inhibition of PKC or its reduced expression may enhance insulin sensitivity and insulin receptor tyrosine kinase activity which can be an effective therapeutic strategy against type 2 diabetes. Protein tyrosine phosphatase-1b (PTP-1b) causes dephosphorylation of insulin receptor and is a negative regulator of the insulin signaling. It enhances insulin activity and is resistant to the development of obesity. PTP-1b down regulates or blocks leptin signaling by dephosphorylating Janus kinase (JAK). Thus PTP-1b serves as an essential therapeutic target. Phosphoinositide 3 kinase (PI3K) plays a significant role in the glucose uptake *via* insulin stimulation and GLUT4 translocation. PI3K is down regulated by two classes of serine/threonine kinases, Akt, also known as protein kinase B (PKB) and the isoforms of PKC[7-10]. Akt and isoforms of PKC are known to facilitate GLUT4 translocation. P70s6k directly phosphorylates IRS (insulin receptor substrate) which inhibits its activity and hinders Akt actively. Mammalian target of rapamycin (mTOR) has a significant role in obesity and IR and activates both Akt and p70s6k. The essential targets for Akt include the transcription factors, glycogen synthase kinase 3 (GSK3) and the forkhead box subgroup O (FOXO). GSK3 can phosphorylate and inhibit GS. Now phosphorylation of Akt inactivates GSK3 and leads to an increase in glycogen synthesis[7-10]. Akt phosphorylation also targets FOXO mediated transcription of target genes that promote the production of β-cells. To counteract IR and restore insulin sensitivity therapeutic agents should target to increase PI3K/Akt activity. Lipid phosphatase PTEN (phosphatase and tensin homolog) dephosphorylates phosphatidylinositol (3,4,5) trisphosphate (PIP3) making it less available to recruit Akt. Also downstream regulation of mTOR can regulate adipogenesis and insulin sensitivity[7-10].

AMPK (AMP activated protein kinase) regulates hepatic gluconeogenesis and increase muscle glucose uptake by translocation of GLUT4 which also serves the purpose of an essential therapeutic target[10]. A comprehensive scheme of the different receptor signaling pathways have been presented below in Figure 1.

Some of the novel molecular targets for anti-diabetic therapy have been mentioned in Table 1.

PHYTOSYNERGY IN TYPE 2 DIABETES

Synergy refers to the increased effectiveness that results when two or more elements work together, though here we will refer to phytochemical constituents. Synergism is the total outcome of a cumulative effect which is greater than the sum of individual effects. From the dimensions of pharmacology, molecular biology or clinical research, synergism can be either in the form of multi target effect where different phyto-constituents of a single extract or a composite extract will affect more than one targets agonistically and exhibit

Table 1 Possible therapeutic molecular targets for type 2 anti-diabetic therapy

Type	Target for action	Nature of action	Effect produced
Protein kinases	Protein kinase C	Inhibitory	Block receptor desensitization
	AMP activated kinase	Activator	Enhance glucose transport
	GSK-3	Inhibitory	Activate glycogen synthase
	MAP kinase	Inhibitory	Block receptor desensitization
Protein phosphatases	PTP-1b	Inhibitory	Block receptor dephosphorylation
	PP1	Activator	Activate glycogen synthase
	LAR	Inhibitory	Block receptor dephosphorylation
Lipid phosphatases	PTEN	Inhibitor	Increase PIP3-stimulated glucose transport
Cell surface receptors	Insulin receptor	Agonist	Insulin mimetic
	Glucagon receptor	Antagonist	Low fasting glucose
	GLP receptor	Agonist	Increase insulin secretion
	β-3 adrenergic receptor	Agonist	Increase lipolysis
Ion channels	Sulphonyl urea receptor	Inhibit K channel	Increase insulin secretion
Transcription factors	PPAR-γ	Selective modulator	Insulin sensitizer
	HNF4	Selective modulator	Increase insulin secretion

AMP: Adenosine monophosphate activated kinase; GSK-3: Glycogen synthase kinase 3; MAP: Mitogen activated protein; PTP-1b: Protein tyrosine phosphatase-1b; PP1: Protein phosphatase 1; LAR: Leukocyte antigen related; PTEN: Phosphatase and tensin homolog; PPAR-γ: Peroxisome proliferator-activated receptor; GLP: Glucagon-like peptide.

synergism[11,12]. Synergy can give better outcomes in terms of pharmacokinetic profile or physicochemical effects based on enhanced solubility profile, improved absorption and ultimately better bioavailability. Use of synergistic combinations also helps to restrict the development of resistance due to single prolonged drug use. While synthesizing or processing a single entity, unwanted adverse effects may develop due to either the extraction procedure or synthetic scheme being followed, or development of any by products; such adverse effects can be minimized or eliminated by use of combo formulations. Moreover stability issues of one to several bio-actives on long storage are more protected in combined form than in isolated form[11,12].

Combination therapy has made its way in the treatment of type 2 diabetes whether it is western classical medicine or herbal formulations. Resveratrol, a phytoalexin found in grapes which acts on various molecular targets in adipocytes and osteoblasts decreases the number of adipocytes and acts synergistically with quercetin and genistein to reduce adipogenesis[12]. Evidence based clinical research results have shown that miglitol in combination with metformin provides a better glycemic control than metformin monotherapy which is an example of synergism in anti-diabetic therapy with western medicine. Oleanolic acid, a pentacyclic triterpene, a natural component of many medicinal herbs in combination with metformin, first line antidiabetic drug showed synergistic anti-diabetic potentials in animal studies[13]. Experimental results showed that the combination reduced hepatic gluconeogenesis by decreasing mRNA expressions of PGC-1α, G-6-Pase and PEPCK (Phosphoenol pyruvate carboxykinase 1). The combination is also found to stimulate the PI3K pathway that phosphorylates Akt and down regulates mTOR to improve insulin resistance. Sesame oil, an edible oil rich in mono and polyunsaturated fatty acids is found to show synergistic anti-diabetic potentials with sulphonyl ureas *viz.* glibenclamide[14]. In case of allopathy, results of clinical trials have shown that combination therapy with miglitol and metformin was found to be more effective than the use of single drug alone[15].

Establishment of standard quality control profile in global context to confirm the validity and reproducibility of phytochemical constituents in the form of processed extract rather than single isolated compound; proper analytical and spectroscopic method development for structural characterizations in combined forms; rigorous validation of safety profile and pharmacokinetic parameters is essential to find a scientific basic of phytosynergy which may give rise to a new generation of medicinal products - phyto-pharmaceuticals[11].

BIOWAIVER-COMPUTATIONAL PHARMACOKINETICS AND IVIVC

Drug development procedure is very tedious and expensive and in many cases due to lack of adequate pharmacokinetic data of the candidate drug, completion of further research becomes questionable. With the vast expansions in the research arenas undertaking the development of new chemical entities, bioequivalence studies are of vital concern in drug development especially when there are absolute new entities or having narrow therapeutic index. Though *in vivo* animal experimentation for establishing the pharmacokinetic profile is still the surrogate, yet it's very tedious, expensive, and time consuming to handle enormous amount of data. Along with the development of *in silico* pharmacology, computational modeling now finds applications in pharmacokinetics and dynamics, as well as toxicokinetics and dynamics. Many multinational pharma R&Ds are now focusing on bio-waiver where in many cases *in vitro* results were considered more acceptable in different dosage formulations especially immediate release solid dosage forms[16-18]. In that condition to proceed with a bio-waiver study there's a need to establish dissolution profile and is to be characterized with both model dependent and independent approaches. *In vivo* performance of a dosage formulation or new chemical entity can be

Table 2 Types of *in vitro-in vivo* correlation and the parameters used

Level	*In vitro* parameters	*In vivo* parameters	Utility
Level A: direct relationship with *in vivo* data based on *in vitro* measurement alone	Dissolution curves	Absorption curves	Highest level of correlation depicting point to point relation between *in vitro* dissolution rate and *in vivo* input rate of drug from dosage form. Marks *in vitro* dissolution as the surrogate of *in vivo* performance
Level B: relation based on statistical moments analysis	MDT	MAT; MRT	Mean *in vitro* dissolution time of the product compared to mean *in vivo* residence time or mean *in vivo* dissolution time
Level C: relates one dissolution time point ($t_{50\%}$, $t_{90\%}$, *etc.*) to one mean pharmacokinetic parameter (AUC, Cmax, tmax)	Disintegration time, time to have 10%, 50%, 90% dissolved, dissolution rate, dissolution efficiency	Cmax, Tmax, Ka, time to have 10%, 50%, 90% absorbed, AUC (total or cumulative)	Single point weak correlation showing a partial relation between absorption and dissolution. Used in early stages of formulation development before pilot production

MDT: *In vivo* measurement of the dissolution rate in the digestive tract; MRT: The mean time that the drug resides in the body, MRT may also be the mean transit time; MAT: The mean time required for drug to reach systemic circulation from the time of drug administration. It is actually the mean time involved in the *in vivo* release and absorption processes as they occur in the input compartment and is estimated as MAT = MRT - MRToral/*i.v.*; AUC: In pharmacokinetics, AUC is the area under the curve (mathematically known as definite integral) in plot of concentration of drug in blood plasma against time, it reflects the actual body exposure to drug after administration of a dose of the drug and expressed in mg × h/L; Ka: It is the absorption rate constant which is a proportionality constant that relates the rate of drug absorbed in the body; Cmax: It refers to peak serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and prior to the administration of a second dose; Tmax: It is the time after administration of a drug when the maximum plasma concentration, Cmax is reached and during which rate of absorption is equal to the rate of elimination. MDT: Mean dissolution time; MAT: Mean absorption time; MRT: Mean residence time.

simulated from the *in vitro* dissolution data after establishing a definitive IVIVC[19-23].

The biopharmaceutics classification system (BCS) proceeds with a predictive approach for developing correlation between physicochemical criteria of drug formulations and its *in vivo* bioavailability. BCS is not the direct IVIVC; IVIVC develops a mathematical relation between *in vitro* and *in vivo* data by either linear or non- linear correlation[19-25]. As per FDA guidelines IVIV correlation ranges from A-D with multiple level C correlation, the details of which have been presented in Table 2.

Apart from these three types of correlation, level D correlation is a rank order and qualitative method which may be applicable in some steps of formulation development but not recommended for regulatory purposes. A multiple point level C correlation is really a justified bio-waiver where correlation is established over the entire dissolution profile with one or more pharmacokinetic parameters of interest. This correlation is based on three dissolution points (early, middle and end stages) and on achievement of this correlation level, the level A correlation is also likely to develop[19-21].

Even after the attainment of high level of correlation, till date no *in vitro* method can exactly simulate physiological conditions *in vivo* especially when it comes to replicate the exact gastro-intestinal (GI) conditions *in vitro viz*. appropriate amount, pH and exact physiological amounts of enzymes needed for digestion, physiological transits during digestion process, exact replication of peristalsis, food - drug interactions and its impact on dosage formulations. An artificial digestive system known as TIM1 have been developed by TNO Nutrition and Food Research mimicking the human stomach and three segments of small intestine where pH is monitored and computer controlled, constant generation of water pressure ensures mixing of enzymes by alternate compression and relaxation of flexible walls and removal of water and small molecules from lumen compartment by pumping dialysis fluid mimics the GI motility. Though such artificial models find applications in nutrition research but to be an effective quality control tool in drug development studies warrants further research[21].

CONCLUSION

Translational health research is the latest buzzword in the field of biomedicine which aims to bridge basic research with medical innovation with the perspectives of sequential development of products from lab bench to patient bedside. The landscape of drug discovery which is just the initiation of creating new chemical entities has undergone a drastic change after the emergence of computational biology, combinatorial chemistry and *in silico* docking studies. Now drug molecules are tailored as per requirements for maximizing bioavailability and stringent control over pharmacokinetics. Combination therapies with synergistic potentials are finding more prominence than monotherapy and even documentations are available in some anti-diabetic medications where combination of natural and synthetic medicine showed better results. However to capture the international pharma market and speed up the pilot scale production, there is an urgent need to boost bio-waivers which necessitates to develop robust and reproducible *in vitro* models simulating *in vivo* conditions.

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