SECTION IV
CONCLUSIONS

9. CONCLUSIONS

Diabetes mellitus, a syndrome consisting of interrelated metabolic, vascular, and neuropathic components; and is defined as a group of metabolic diseases that are characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Human type I diabetes mellitus (IDDM) is caused by an absolute deficiency of insulin secretion resulted from T cell-mediated, autoimmune destruction of pancreatic β-cells or by a primary defect in β-cell function secondary to another (nonautoimmune) cause. In type II diabetes mellitus (NIDDM), the cause of the heterogeneous disease is a combination of factors including insulin resistance at the level of the muscle and liver, and an inadequate insulin secretory response.

Glipizide, a representative of the second generation sulfonylureas and appears to be the most effective insulin secretogogue both in first phase insulin secretion and in sustained stimulatory response during long term administration. A decrease in blood glucose concentration level occurs within 30 min of ingestion of glipizide, providing peak plasma level concentrations within 1–3 h after a single oral dose with an elimination half-life ranging from about 2 to 4 h. Nateglinide, a D-phenylalanine derivative acts by binding to the sulphonylurea receptor to inhibit K_{ATP} channels in pancreatic β-cells, which results in calcium influx and subsequent insulin release. As plasma glucose rises, β-cell sensitivity to nateglinide increases and insulin release amplifies. Following ingestion, it is absorbed rapidly (within 30 min) with a maximum plasma concentration occurring within one-half to two hours (t_{max}, 1.5 ± 1.1 h) and has very short half-life of 1-1.25 h. Such a rapidly absorbed drugs having faster elimination rate with short half-life make them suitable candidates to be formulated for the sustained delivery.

An active substance cannot meet patient's needs without an appropriate formulation. Formulation development activity is not only restricted to new chemical entities but also improvement of drug delivery of existing drugs. Pharmaceutical dosage form development results in a dosage form that is efficacious, patient friendly, stable and delivering the drug with minimal adverse effects as closely as possible to the intended target. The pharmaceutical companies are increasingly seeking innovative dosage forms for expanding markets and indications, extending product life cycles and generating newer opportunities. Two broad reasons for companies to look at new dosage form development as a strategy for growth are: commercial compulsions and technological advances.

In recent years, controlled/sustained/modified release dosage forms have increasingly gained popularity over other conventional dosage forms in treating diseases as the therapeutic efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement within the body. Moreover, they reduce the size and number of doses, reduce total disease management cost, thereby providing economic merit to the society and improve patient compliance. Most sustained release drug delivery systems developed are aimed at slowing the apparent absorption rate by reducing drug release rate from the dosage form. The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel approaches or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more a design property of a rate-controlled dosage form, and less, or not at all, a property of the drug molecule's inherent kinetic properties. The oral route is by far the most popular route of drug administration for both conventional and novel drug delivery systems. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package, and shipment; increased stability and virtual tamper resistance. Patients overwhelmingly prefer solid oral dosage over other drug forms due to simple, easy, convenient and safe self administration.

In addition, hydrophilic monolithic swellable matrix systems are among the most widely used means for sustained drug delivery in solid oral dosage forms, as they are more forgiving of variations in ingredients, production method and relatively easy to formulate with existing, conventional equipments, and processing methods. Moreover, it results in more uniform release profiles with a high resistance to dose dumping. Matrix systems can be conveniently prepared by using simple polymer fabrication techniques involving a physical blending of the active agent with a polymer matrix, followed by direct compression into a tablet form. Ultimately, matrix systems are economic to the manufacturers as well as to the patients also.

Hence, the research work was aimed to design and evaluate the sustained release oral dosage forms (matrix tablet) of glipizide and nateglinide by direct compression method.

Analytical methods for the estimation of glipizide and nateglinide - the spectroscopic (for routine analysis and in vitro dissolution study) and HPLC (for estimation of drug from biological samples of in vivo study) were developed and optimized. They were also validated in accordance with the ICH guidelines. Spectroscopically, glipizide (at 276 nm) and nateglinide (at 210 nm) were quantified in phosphate buffer pH 6.8 in the analytical range of 1-50 µg/ml with

regression co-efficients of 0.9997 and 0.991, respectively. For quantification by HPLC method, glipizide (at 225 nm) and nateglinide (at 203 nm) were separated using acetonitrile : phosphate buffer pH 3 (70:30 v/v) as a mobile phase on C_{18} reversed phase column at flow rate of 1 ml/min. The retention time for glipizide, gliclazide (internal standard for both the drugs), and nateglinide and were 3.5, 4.7, and 5.7 respectively. The methods for both the drugs were found to be linear within 10-2500 ng/ml with extraction efficiency of more than 97% from the plasma samples. The LoD and LoQ for glipizide were found to be 2.64 and 8.8 ng/ml whereas those for nateglinide were 2.91 and 9.7 ng/ml, respectively. The method was found to be accurate (98-101%) and precise (RSD < 2%) for both the drugs and successfully applied for the quantification of drugs from plasma samples during in vivo study.

Drug-excipient interaction studies were carried out to check the compatibility of the matrix components using differential scanning calorimetry (DSC). The results of the DSC study indicated the suitability of both the drugs with different combination of excipients used in different formulations without any signs of interactions. The physical mixtures of the matrix components were evaluated for their suitability for direct compression by calculating the Carr's index (I_c, in the range of 5-18%), Hausner ratio (R_H, below 1.25), and angle of repose (θ, between 20-42°) for each batch. Uniformity of the mixing was assessed by conducting content uniformity test (95-105%) on the samples of the powder mixture before tabletting by direct compression. Prepared hydrophilic matrices containing different combination of polymers and excipients were evaluated for weight variation, thickness, diameter, hardness, drug content (95-105% of the label claim), in vitro drug release profiles (should be within the constraints defined at all time points) and finally optimized batches were subjected to stability studies as per ICH guidelines. In vitro drug release profiles of all the prepared batches were subjected to fit into different kinetic drug release modalities such as zero-order, first-order, Higuchi's square root of time equation, Korsemeyer-Peppas' power law equation, and Hixson-Crowell's cube root of time equation. The goodness of fit was evaluated by comparing the regression co-efficient. The change in matrix tablet composition was correlated to the respective shifts/deviations in drug release kinetics. The release profiles of glipizide containing optimized sustained release batches were compared to that of the marketed sustained release formulation glytop-10 SR using similarity factor (f_2). In addition, the optimized batches of both the drugs were further subjected to swelling study, Kopcha model analysis and SEM study to confirm the drug release mechanisms.

For the sake of simplicity, the prepared matrices were divided into groups depending on the matrix former polymer used in the formulations.

Glipizide Matrices:

Different combinations of HPMC, MCC, Starch 1500, and lactose at different polymer ratios (M-1 to M-35) were checked for their ability to retard glipizide release. The effects of HPMC viscosity grades, MCC particle size, and compression force (effect of tablet hardness) on the drug release were also investigated. The increase in viscosity of HPMC reduces the mobility of water molecules within the gel layer and hence greater diffusional resistance leads to decreased drug release in the order of HPMC K100LV > K4M > K15M > K100M. MCC PH301 hydrates more quickly and promotes the drug release due to its lower particle size as compared to that of MCC PH302. Addition of water-soluble lactose creates channel by promoting the entry of dissolution medium within the matrix and thereby increases drug diffusion rate. Use of starch changes the release profiles depending on its proportion in matrix. Due to its swelling power and super-disintegrant nature, it raises initial drug release but latter on synergistically contributes with HPMC to sustain the drug release. From this group of matrices, combination of HPMC K4M and MCC PH301 could sustain the drug release for 12 hours and hence this combination was studied by 3^2 full factorial experimental design using HPMC K4M : MCC PH301 ratio and tablet hardness as the formulation variables. Measured responses were cumulative percentage glipizide dissolved at 2, 4, 6, 8, 10, and 12 hour (Q_t). Responses surface were generated for individual response variables and overlapped to select the optimized region within which the matrices give desired release profile. Formulations M-3 (HPMC K4M : MCC PH301 at 25:75) and M-25 (HPMC K4M : MCC PH301 : Starch 1500 at 25:30:45) were found to be optimized. Drug release kinetic data suggests that glipizide release from M-3 was combination of diffusion and erosion both (initially erosion prevails and later on diffusion predominates) while for M-25, diffusion was the main drug release mechanism. Both formulation release profiles fit into Korsemeyer-Peppas kinetics and glipizide release occurs by non-fickian anomalous transport mechanism.

Directly compressed MCC-alginate matrices with and without gel promoter dibasic calcium phosphate, disodium hydrogen phosphate, calcium gluconate, and chitosan (M-36 to M-47) were prepared to prolong the active drug release. Presence of cations can improve gel strength and increased the mean dissolution times - MDT_{50} and MDT_{80} to some extent, but chitosan prepared extremely strong ionotropic gel that released only about 50 % of the matrix dose within 12 hours.

None of the formulation studied in this group passed the dissolution constraints. Glyceryl behenate was not found suitable for direct compression.

Ethylcellulose was also tried as a drug release modifier (M-52 to M-61). Suppression of initial drug release rate was attributed to its hydrophobic characteristic which, delayed dissolution media penetration. However, after 4 hour, HPMC developed viscous gel that controlled drug release throughout dissolution study. Guar gum matrices were difficult to compress because of its poor carr's index value. Xanthan gum successfully controlled the drug release (M-68-76) when tried in combination with different directly compressible excipients. Batch M-70 (xanthan : MCC PH301 at 70:40) and M-75 (xanthan : HPMC K4M : Starch 1500 at 70:25:15) released glipizide in controlled manner and passed the constraints determined at all time points. Water uptake of both matrices was around 1000 to 1200 % of its original weight. M-70 followed Korsemeyer-Peppas kinetics and drug release was mainly by diffusion of glipizide through the hydrated viscous gel barrier. While dissolution profile of M-75 fitted in first order kinetics and drug release was initially erosion mediated and later on by combination of diffusion and erosion.

Carbopol, anionic polymeric material was investigated to modify the drug release depending on the change in viscosity grades and in combination with other excipients (M-77 to M-97). Carbopol gained water (up to ~600%) upon hydration and free carboxylic groups induced repulsion between like negative charges, which resulted in extended carbopol gel structure. It causes drug release due to increase in osmotic pressure within the matrix upon swelling, and sloughing off discrete pieces of hydrogel. Addition of lactose in carbopol matrices increases drug release due to its water-soluble nature. Carbopol 931P : MCC PH301 at 70:30 ratio (M-84) was found optimum to give desired drug release rate by fickian diffusion and its drug release profile was best fitted to Korsemeyer-Peppas model. Presence of pores in the SEM images confirmed the drug release by diffusion.

Kappa-carrageenan (Gelcarin GP-911) formed rigid and brittle gel, which disintegrated and complete drug release occurred within 20 min. On the other hand, iota-carrageenan (Gelcarin GP-379) formed elastic and cohesive gel that was capable to retard the drug release. Moreover, addition of the KCl further prolonged mean dissolution time. Though none of the batch (M-98 to M-117) resulted with optimized dissolution profiles, the carrageenan matrices extended glipizide release about 5-11 hours depending on the matrix composition.

Eudragits are polymethacrylate polymers, and actively contributed in drug release kinetics by its unique polymer particle erosion mechanism from different matrices (M-118 to M-129). Unlike the other eroding tablets, which dissolved completely during the dissolution test, a turbid solution or suspension was formed during the

drug release study of tablets showing polymer particle erosion. Eudragit S100 had poor compressibility and was not able to sustain drug release efficiently. However, Eudragit L100 showed good direct compression properties and two combinations in this group were found optimized. The dissolution profiles of M-120 (Eudragit L100 : HPMC K4M at 75:25) and M-126 (Eudragit L100 : HPMC K4M : Starch 1500 at 50:40:10) when subjected to Kopcha model analysis, revealed that erosion was the mechanism responsible for glipizide release. SEM also supported the drug release phenomenon by the presence of rough eroded matrix surfaces.

Alginate (Protonal LF 120M) was further tried to reduce drug release rate by combining it with HPMC K4M or Carbopol 931P (M-130 to M-144). However, unfortunately not a single formulation could extend the drug release more than 6-8 hours at polymer ratios selected for study.

Nateglinide Matrices

From the group of HPMC, MCC, starch containing matrices, two batches J-11 (HPMC K4M : MCC PH301 at 62.5:187.5) and J-16 (HPMC K4M : MCC PH301 : Starch 1500 at 50:60:90) were the optimized batches and their in vitro dissolution profiles best fit into Korsemeyer-Peppas drug release kinetics with non-fickian anomalous transport mechanism. Nateglinide was released from matrices by systemic synchronization between diffusion and erosion depending on the drug : polymer ratio and matrix composition. The smooth hydrogel surfaces with pores in SEM images further supported the release mechanism.

Combination of hydrophobic EC 7FP Premium with swellable MCC PH 301 extended the drug release effectively by non-fickian anomalous transport mechanism. As the EC/MCC ratio decreases, the drug releases kinetic shifts from Hixson-Crowell to Korsemeyer-Peppas model. Batch J-20, (EC 7FP Premium : MCC PH301 at 100:100) was one of the optimized formulation in this group of matrices.

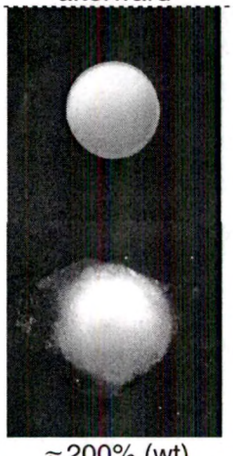
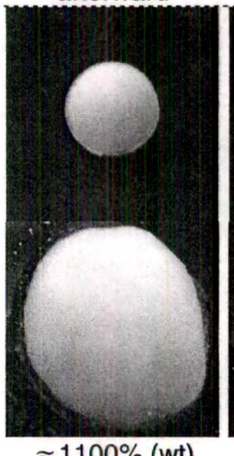
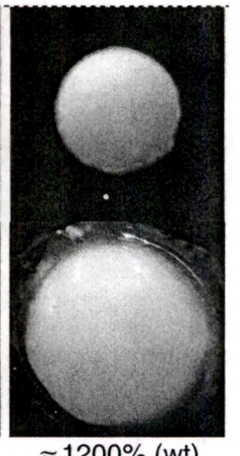
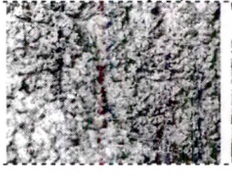
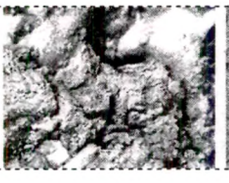
Hydrophilic gel former Carbopol 934P was combined with erosion promoter Eudragit L100 at different ratios to get insight of the drug release mechanism. Eudragit, by its polymer particle erosion properties, controlled the matrix erosion and released nateglinide throughout 12 h from the viscous carbopol hydrogel. Partial substitution of eudragit by starch also resulted in similar drug release profiles as well as made formulation cost-effective. Matrix J-21 (Carbopol 934P : Eudragit L100 at 70:130) and J-23 (Carbopol 934P : Eudragit L100 : Starch 1500 at 80:80:40) showed about 600 % of water uptake and their Kopcha model analysis indicated erosion predominance which was also confirmed by SEM analysis.

Upon hydration, xanthan gum formed tortuous gel layer, which was strong enough to sustain the diffusion of drug, and resulted in linear dissolution profiles. J-34 formulation (Xanthan gum : Eudragit L100 : EC 7 FP Premium at 75:35:40) successfully controlled nateglinide diffusion with the least total polymer level as compared to other matrices. Drug release from this matrix followed Korsemeyer-Peppas kinetics with non-fickian anomalous transport mechanism.
Eudragit L100 also showed polymer particle erosion initially from HPMC hydrogels and anisotropic swelling of matrices (more axial swelling as compared to radial swelling). However, once the hydrogel gained enough viscosity, it diminished the erosion and drug release was controlled by diffusion of drug through HPMC hydrogel. J-42 (Eudragit L100 : HPMC K4M at 114:61) and J-44 (Eudragit L100 : HPMC K4M : Starch 1500 at 80:40:80) formulations passed the in vitro dissolution constraints at all time points and found to be optimized.
The list of the optimized batches with their formulation code, matrix composition, and best fit drug release kinetic model, other in vitro parameters along with in vivo parameters are enumerated in Table 9.1 and Table 9.2 for glipizide and nateglinide, respectively. All these listed directly compressed matrices are promising sustained release oral dosage forms for administration of glipizide and nateglinide in view of their swelling, water uptake, synchronized diffusion-erosion phenomenon, and active drug delivery rate.

In Vivo Studies

Pharmacokinetic parameters for glipizide containing matrices M-3 (HPMC K4M : MCC PH301 at 25:75), M-25 (HPMC K4M : MCC PH301 : Starch 1500 at 25:30:45), M-75 (xanthan gum : HPMC K4M : Starch 1500 at 70:25:15), and M-120 (Eudragit L100 : HPMC K4M at 75:25) were compared with that of the marketed sustained release formulation Glytop® 2.5 SR. Out of the 9 batches (A-1 to A-9) of HPMC K4M : MCC PH301 system studied using 3^2 full factorial design, three batches namely A-3, A-6 ($\approx$ M-3), and A-4 exhibited the slow, medium, and fast release profile, respectively, and hence were selected for establishment of IVIVC according to US FDA guidelines. The rapid decrease in glipizide concentration after oral solution administration reflects the fast disposition and elimination of the drug. The pharmacokinetic parameters like C_{max} and *MRT* as well as the plasma concentration–time profiles of glipizide explicitly indicate that all three matrix tablets sustained the absorption of glipizide as compare to oral solution. The C_{max} and k_a for A-3 < A-6 < A-4, and *MRT* for A-3 > A-6 > A-4, which reflect the difference in the release rate kinetics of glipizide between them. Similarly, results of in vivo study of nateglinide containing matrices J-11 (HPMC K4M : MCC PH301 at 62.5:187.5) and J-21 (Carbopol

Table 9.1. Comparison of various in vitro and in vivo parameters for optimized hydrophilic matrices of glipizide.

Batch No.	M-3	M-25	M-70	M-75
Composition	HPMC K4M:MCC PH301	HPMC K4M:MCC PH301:Starch 1500	Xanthan gum:MCC PH301	Xanthan gum:HPMC K4M:Starch 1500
Proportion	25:75	25:30:45	70:40:00	70:25:15
Tablet weight	113	113	123	123
Best fit Model	Korsmeyer-Peppas	Korsmeyer-Peppas	Korsmeyer-Peppas	Zero order
f_2 (w.r.t. Glytop 10 SR)	66.34	52.62	53.31	63.45
Release mechanism by Kopcha model	Predominant erosion up to 6 h, diffusion afterward	Predominant diffusion throughout	Predominant erosion up to 2 h, diffusion afterward	Predominant erosion throughout
0 h Swelling 24 h		-		
	≈200% (wt)		≈1100% (wt)	≈1200% (wt)
SEM after 12 h dissolution				
$AUC_{0-\infty}$ (ng·h/ml)	2526.04	2547.12	-	2754.57
C_{max} (ng/ml)	192.49	192.49	-	191.36
T_{max} (h)	6	6	-	6
MRT (h)	9.1	9.04	-	9.72
k_a (h^{-1})	0.32	0.32	-	0.3
k_e (h^{-1})	0.19	0.19	-	0.16
Shelf-life	2.84	2.91	2.69	2.78

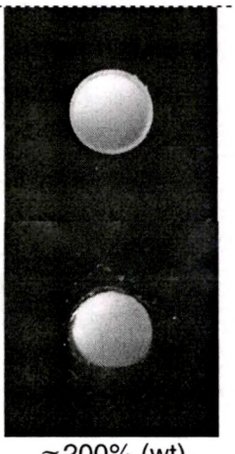
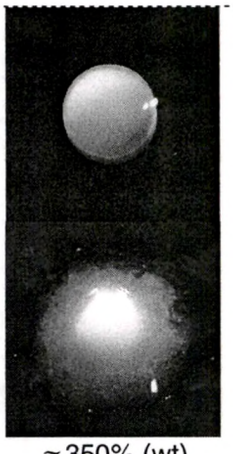
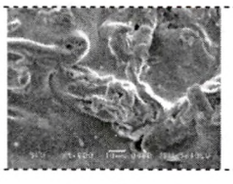
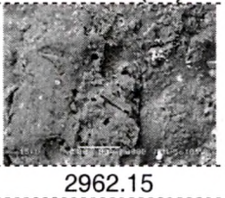
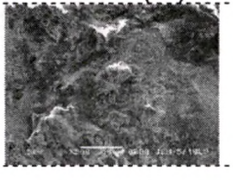
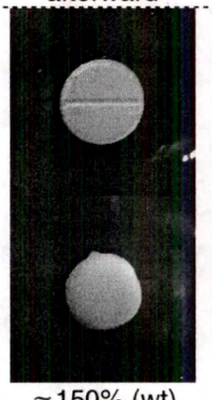
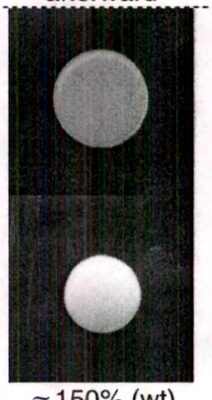
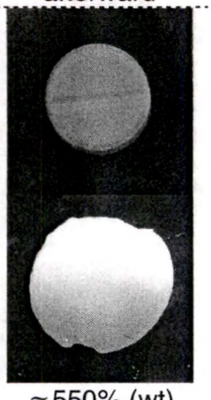
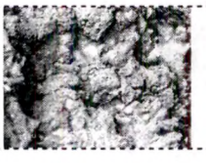
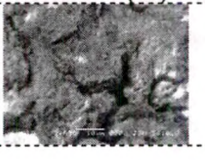
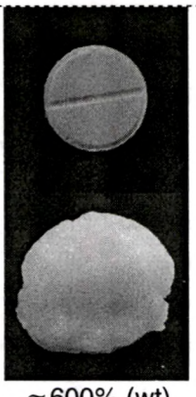
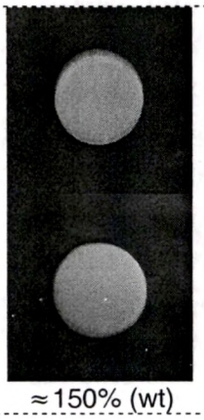
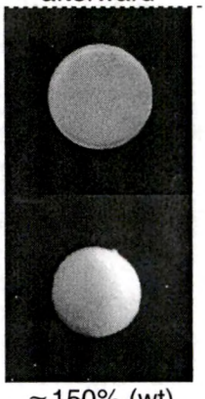
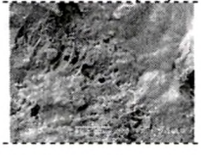
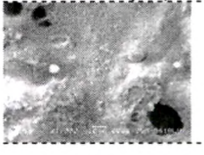
Batch No.	M-84	M-120	M-126
Composition	Carbopol 934P:MCC PH301	Eudragit L100:HPMC K4M	Eudragit L100:HPMC K4M:Starch 1500
Proportion	70:30:00	75:25:00	50:40:10
Tablet weight	113	113	113
Best fit Model	Korsmeyer-Peppas	Zero order	Korsmeyer-Peppas
f_2 (w.r.t. Glytop 10 SR)	48.50	60.16	62.28
Release mechanism by Kopcha model	Predominant diffusion throughout	Predominant erosion throughout	Predominant erosion throughout
Swelling 0 h 24 h	-	 ≈200% (wt)	 ≈350% (wt)
SEM after 12 h dissolution			
$AUC_{0-\infty}$ (ng·h/ml)	-	2962.15	-
C_{max} (ng/ml)	-	239	-
T_{max} (h)	-	10	-
MRT (h)	-	10.03	-
k_a (h^{-1})	-	0.29	-
k_e (h^{-1})	-	0.18	-
Shelf-life	2.59	2.97	3.12

Table 9.2. Comparison of various in vitro and in vivo parameters for optimized hydrophilic matrices of nateglinide.

Batch No.	J-11	J-16	J-20	J-21
Composition	HPMC K4M:MCC PH301	HPMC K4M:MCC PH301:Starch 1500	EC 7 FP:MCC PH301	Carbopol 934P:Eudgagit L100
Proportion	62.5:187.5	50:60:90	100:100	70:130
Tablet weight	436	386	386	386
Best fit Model	Korsmeyer-Peppas	Korsmeyer-Peppas	Korsmeyer-Peppas	Korsmeyer-Peppas
Release mechanism by Kopcha model	Predominant diffusion throughout	Predominant erosion up to 7 h, diffusion afterward	Predominant erosion up to 2 h, diffusion afterward	Predominant erosion up to 7 h, diffusion afterward
0 h Swelling 24 h	-			
		≈150% (wt)	≈150% (wt)	≈550% (wt)
SEM after 12 h dissolution				
$AUC_{0-\infty}$ (ng·h/ml)	2307.12	-	-	2244.14
C_{max} (ng/ml)	175.66	-	-	185.78
T_{max} (h)	4	-	-	6
MRT (h)	8.52	-	-	8.4
k_a (h^{-1})	0.35	-	-	0.37
k_e (h^{-1})	0.27	-	-	0.26
Shelf-life	2.73	2.87	3.06	2.64

Batch No.	J-23	J-34	J-42	J-44
Composition	Carbopol 934P:Eudgagit L100:Starch 1500	Xanthan gum:EC 7 FP:Eudragit L100	Eudragit L100:HPMC K4M	Eudragit L100:HPMC K4M:Starch 1500
Proportion	80:80:40	75:30:45	61:114	80:40:80
Tablet weight	386	336	361	386
Best fit Model	Zero order	Korsmeyer-Peppas	Korsmeyer-Peppas	Higuchi (Matrix)
Release mechanism by Kopcha model	Predominant erosion throughout	Predominant erosion up to 4 h, diffusion afterward	Predominant diffusion throughout	Predominant erosion up to 4 h, diffusion afterward
Swelling 0 h / 24 h	 ≈600% (wt)	-	 ≈150% (wt)	 ≈150% (wt)
SEM after 12 h dissolution			-	
$AUC_{0-\infty}$ (ng·h/ml)	-	-	-	-
C_{max} (ng/ml)	-	-	-	-
T_{max} (h)	-	-	-	-
MRT (h)	-	-	-	-
k_a (h^{-1})	-	-	-	-
k_e (h^{-1})	-	-	-	-
Shelf-life	2.98	3.17	2.95	3.22

934P : Eudragit L100 at 70:130) were compared with that of marketed immediate release formulations Natelide® 60. A good linear point-to-point relationships were observed for all studied formulations with slope approaching to unity, indicating a close correlation between the in vitro release rate with their in vivo absorption. The results of internal predictability revealed that the predicted profiles were comparable to the observed profiles for all three formulations. According to it, the permissible % prediction error (PE) values for C_{max} and *AUC* should be less than ±15% for each product. The established 'level A' IVIVC confirms the efficacy of this in vitro model in simulating in vivo conditions.

In short, for each matrix former polymer, at a fixed polymer level, the viscosity of the particular polymer grade selected governs the performance of the matrix by affecting the diffusional and mechanical characteristics of the gel. The viscosity inducing polymers such as HPMC, carbopol, xanthan gum, mixture of chitosan-alginate were also deemed to be essential not only for development of resistant gel barrier but also for maintaining tablet integrity. The release of the drug was primarily controlled by the amount of the gelling polymers, except that a minimum amount of viscosity increasing polymer was necessary to hold the matrix together while swelling. The presence of hydrophobic component in the polymer blend retarded matrix hydration and increased MDT_{50} and MDT_{80} and vice versa for hydrophilic excipients. The differences in release rates caused by various co-excipients may be attributed to the changes in matrix porosity and dissolution or permeability of these materials through hydrated gel layer. The structural features of the gel layer are related to the kinetics and mechanism of both water uptake (swelling) and drug release. Almost linear drug release from optimized hydrophilic matrices has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer. Popularity of all these used polymers stem from their non-toxic nature, ease of direct compression, ability to accommodate a large percent of drug and negligible influence of the processing variables on drug release rate kinetics. The release rate of both the drugs can be regulated by utilizing suitable amounts and ratio of polymers and co-excipients, these preparations showed potential in terms of their release kinetics because they released appropriate glipizide and nateglinide fractions as per predetermined constraints within 12 hours. Taken all together, formulations can be manufactured using conventional pharmaceutical processes and equipment. Moreover, they successfully sustained the absorption of glipizide and nateglinide when compared with market samples, suggesting that all optimized directly compressed hydrophilic matrices achieved the complete dissolution and absorption of active drug due to unique performance abilities of different polymeric combinations.

It was concluded from this study that the in vitro dissolution behavior was reflected in the in vivo data for the prototype formulation prepared as per this technology. Significant in vitro–in vivo correlation was obtained, which could be considered bioindicative. Thus, the technology described in this study has the potential to be used in the design of directly compressed sustained release formulations. After internal validation of developed IVIVC model, in vitro dissolution method might be used as a surrogate for human bioequivalence studies. An in vitro dissolution test can replace absorption studies during the pre-approval process, to develop a desirable formulation, and to ensure batch-to-batch bioequivalence. It could also be extremely useful in performing possible post-approval changes in the formulation scale-up or changes in the drug substance or excipient supplier.