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ORIGINAL ARTICLE

Statistical significance of polymeric physicochemical properties in the development of formulations containing a drug from neutral class

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Abstract The main objective of the present study was to develop quantitative-structure property relationship (QSPR) models with predictability for release, transportability and related properties of formulation containing a neutral drug (glimepiride) based on polymeric properties. Such physicochemical properties are measure of polymers' behavior in deciding release, transportability and bioavailability of drug. Therefore comprehensive study of properties could help in deciding proper polymer composite for formulation with required characteristics. A total of nine glimepiride (GLMP) tablet batches were prepared using three polymers representing extended, moderate and immediate release categories. Molecular descriptors were calculated from polymeric structures and correlated with formulation characteristics. This leads to generation of predictive models. Compatibility between drug-excipients was confirmed. Weight uniformity, drug content, hardness and friability tests showed acceptable results. In vitro dissolution kinetics exhibited Korsmeyer-peppas model as best fit. Best correlation coefficient and validation of developed QSPRs showed powerful predictability for properties. Transportability was influenced by release rate together with molecular size, p*K*a, log *P* and water solubility of GLMP. Generated models were found to significantly predict the release, transportability and related formulation properties. QSPR models were developed with enough prediction potential for the properties of formulation containing any neutral

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drug and could also help to decide the formulation composition for required characteristics together with pharmacoeconomic impact with respect to time, cost and material.

1. Introduction

Polymeric excipients are commonly incorporated in the formulation for attaining a site specific delivery of the drug in more controlled and effective way along with the improved physical appearance of formulation and drug protection from biological media before its release (Arifin et al., 2006; Langer and Peppas, 1983; Borgquist et al., 2006). Therefore, physicochemical properties of polymer as indicative of its wettability and hence the drug dissolution, must be studied extensively before selection of any polymer for desired drug delivery system (Grover et al., 2000a, 2000b). By using QSPR approach such physicochemical properties or descriptors representing polymer structure can also be calculated theoretically and can be subsequently correlated with formulation characteristics (Grover et al., 2000a, 2000b; Gafourian et al., 2007). This could help in the development of QSPR models with potential predictability for required property based on polymeric properties showing significant influence on formulation characteristics (Wu et al., 2005). Developed model could help in deciding and optimizing the appropriate polymer composite and hence the formulation composition with required characteristics (Siepmann et al., 2010). Moreover, the release, transportability and related formulation properties would also become predictable theoretically for other drugs from the neutral class and from other polymers with matching physicochemical properties (Gafourian et al., 2007). Therefore, QSPR approach will help in the future formulation development work through the deciding composition of formulation in a more systematic and theoretical way for desired characteristics with saving of time and cost of pharmaceutical industry (Arifin et al., 2006; Gaikwad and Bhatia, 2013; Wu et al., 2005).

The present study was designed with the main objective to develop a predictive mathematical model through correlation analysis between polymeric descriptors and properties of a formulation containing a neutral drug. A total of nine tablet batches of GLMP (model drug from neutral class) were prepared using three polymers representing synthetic or cellulose semi-synthetic class from each extended, moderate and immediate release category. Prepared compacts were further evaluated for several post-compression properties such as compatibility, weight uniformity, drug content, hardness, friability and *in vitro* drug release and transportability studies.

2. Materials and methods

2.1. Materials

GLMP was a generous gift from USV Limited (Mumbai, Maharashtra, India). Evonik industries (Mumbai, Maharashtra, India) provided Eudragit RS100 (ERS100) as a gift sample. Methocel E15 LV premium (ME15) and Ethocel 10 cp FP standard premium with 48.0–49.5% ethoxyl content (EC10) were kindly obtained from Colorcon Asia Pvt. Ltd. (Goa, India) as gift samples. Hydroxypropyl cellulose (HPC, Innovative Chemicals, Mumbai, Maharashtra, India); Crospovidone (CPVP, S.D. Fine-Chem Ltd., Mumbai, Maharashtra, India); Croscarmellose sodium (CCS, S.D. Fine-Chem Ltd., Mumbai, Maharashtra, India); Sodium starch glycolate (SSG, S.D. Fine-Chem Ltd., Mumbai, Maharashtra, India); Polyethylene glycol 6000 (PEG 6000, Research Lab, Mumbai, Maharashtra, India); Carboxymethyl cellulose sodium (CMCS, Loba Chemie Pvt. Ltd., Mumbai, Maharashtra, India) were purchased. Research Lab (Mumbai, Maharashtra, India) supplied starch, lactose, fumed silica and magnesium stearate. HiMedia Laboratories Pvt. Ltd. (Mumbai, Maharashtra, India) supplied dialysis membrane (Dialysis Membrane – 110). All other ingredients and chemicals used were of analytical grade or higher.

2.2. Methods

2.2.1. Characterization of drug and excipients

2.2.1.1. Standard curve. GLMP identification was done within scanning range of 200–400 nm by using UV–Visible spectrophotometer (Shimadzu Corporation, UV-1800, Japan). A standard curve was obtained separately in hydrochloric acid buffer pH 1.2 *USP* (USPNF, 1995) and phosphate buffer pH 6.8 *USP* (USPNF, 1995) at observed λ_{maxs} for GLMP.

2.2.1.2. Fourier transform infrared spectroscopy (FTIR) studies. Compatibility testing between pure drug (GLMP) and other excipients was accomplished by using recording Jasco FTIR-4100 Spectrometer within scanning range of 400–4000 cm^{-1} at a resolution of 1 cm^{-1}. FTIR analysis was done using a KBr method (1:100; sample:KBr ratio) to examine any chemical or structural changes in GLMP in tablet formulations.

2.2.2. Formulation of compacts

As per composition shown in Table 1, a total of nine batches of GLMP granules (GMR1 to GMO3) was prepared by wet granulation technique. Initially uniformly sized powder mass was obtained by sieving all ingredients separately through a mesh with 180 μm size (ASTM #80). Further distilled water was added as a granulating liquid to convert uniformly mixed powdered mass into wet mass (except batch GMB2 and GMO3). The wet mass was passed through mesh size 850 μm (ASTM #20) to obtain granules which were further dried in a hot air oven (Bio Technics India, Mumbai, Maharashtra, India) at 60 °C for 1 h. After drying, the granules with narrow size distribution were selected by passing through mesh size 600 μm (ASTM #30) and subsequently mixed with glidant (fumed silica or aerosil) and lubricant (magnesium stearate) for compression into tablets.

Table 1 Composition of GLMP tablet formulations.[a]

Ingredients	Batch code								
	GMR1	GMR2	GMR3	GMB1	GMB2	GMB3	GMO1	GMO2	GMO3
SSG	300	–	–	–	–	–	–	–	–
CCS	–	300	–	–	–	–	–	–	–
CPVP	–	–	300	–	–	–	–	–	–
ME15	–	–	–	300	–	–	–	–	–
PEG 6000	–	–	–	–	300	–	–	–	–
CMCS	–	–	–	–	–	300	–	–	–
EC10	–	–	–	–	–	–	300	–	–
HPC	–	–	–	–	–	–	–	300	–
ERS100	–	–	–	–	–	–	–	–	300
Aerosil	13	13	13	13	13	13	13	13	13
Magnesium Stearate	25	25	25	25	25	25	25	25	25
Lactose	23	23	23	23	23	23	23	23	23
Starch	35	35	35	35	35	35	35	35	35
Total weight of compact (mg)	400 ± 5	400 ± 5	400 ± 5	400 ± 5	400 ± 5	400 ± 5	400 ± 5	400 ± 5	400 ± 5

[a] All quantities are given in mg. Each tablet contains 4 mg of GLMP.

Compacts with constant hardness of 4–5 kg/cm^2 were prepared by compressing the dried granules [400 ± 5 mg containing 4 mg of GLMP (IP, 2010a; Reichal et al., 2011; Patel et al., 2012; Choudhary and Bajpai, 2011)] by using a 8-punch rotary tablet press machine (CIP Machineries Pvt. Ltd., Ahmadabad, Gujarat, India) having a 10-mm round, flat-faced punch and die set. Tablets were further kept at ambient conditions for the 24 h relaxation period for elastic recovery and hardening effect (Krycer et al., 1982). Subsequent to relaxation period tablets from all batches were characterized for various post-compression evaluation parameters: drug content, weight uniformity, diameter, thickness, friability, hardness and *in vitro* dissolution and transportability studies.

2.2.3. Evaluation of tablet formulations

2.2.3.1. Weight uniformity. By using an electronic balance (AUX220, Shimadzu Corporation, Japan) a total of randomly selected 20 tablets for each batch (GMR1 to GMO3) were weighed separately and compared with average weight for calculation of % deviation. Tablets comply with the weight uniformity test if not more than two of the individual tablet weights deviate from the average weight by more than ±5% (for 250 mg or more) (IP, 2010b; Banker and Anderson, 1987).

2.2.3.2. Drug content. For estimation of GLMP content, weigh and powder not less than 10 tablets individually from each batch (GMR1 to GMO3). Accurately weigh a quantity of powder equivalent to 4 mg of GLMP (tablet dose) and dissolve in sufficient amount of methanol and volume was made up to 100 mL with phosphate buffer pH 6.8 *USP* (Wagh et al., 2012; Sahu, 2010). The resulting solution was filtered using Whatman filter paper no. 42 and after suitable dilutions, analyzed by UV–Visible double beam spectrophotometer (Shimadzu Corporation, UV-1800, Japan) at 227 nm against methanol:phosphate buffer pH 6.8 *USP* as a blank. The GLMP content of the tablet was further determined using the linearity equation obtained from the calibration curve. Drug content of all tablet formulations was tested in triplicate (n = 3) (Wagh et al., 2012; Sahu, 2010).

2.2.3.3. Hardness. Hardness or crushing force required to break the compact was determined by using Monsanto-type hardness tester (Lab Hosp Corporation, Mumbai, Maharashtra, India) for not less than 3 tablets from each batch (GMR1 to GMO3). Tablet hardness was measured by holding the tablet diametrically between mobile and fixed surface of tester and then indicator scale was set to zero. Subsequently the force (kg/cm^2) was applied gradually to forward move of the screw knob until tablet breaks.

2.2.3.4. Friability. Friability of tablets from each batch (GMR1 to GMO3) was determined using Roche friabilator (Electrolab, Mumbai, Maharashtra, India). Pre-weighed sample of randomly selected 10 tablets was subjected to friability testing by transferring it into a plastic chamber rotating for a total of 100 revolutions at 25 rpm for 4 min. This resulted into the tablet drop across the height of 6 in. in each revolution with the combined effect of shock and abrasion (USPNF, 2006a). Subsequently tablets were de-dusted for removal of fines adhered to the tablet surface during the test and reweighed. Friability (F) was then calculated using Eq. (1). Each batch (GMR1 to GMO3) was evaluated in triplicate for friability testing ($n = 3$).

$$F = \frac{W_i - W_f}{W_i} \times 100. \quad (1)$$

where W_i and W_f are the initial and final tablet weights. Selected tablet sample passes the friability test if not more than 1% weight loss was observed (USPNF, 2006a).

2.2.3.5. Uniformity of thickness and diameter. By using digital vernier calliper the crown-to-crown thickness and diameter of minimum three tablets selected randomly from each batch were measured at 3 different points of each tablet. The variation limits for both thickness and diameter of tablets allowed are ±5% of the tablet size (Banker and Anderson, 1987).

2.2.3.6. In vitro drug release kinetics. Dissolution testing for all tablet formulations (GMR1 to GMO3) of GLMP was performed as per the procedure described in the individual

monograph USP (USPNF, 2011) and in General Chapter Dissolution ⟨711⟩, USP (USPNF, 2006b) as described below.

Prepared tablets (400 ± 5 mg) from all formulation batches were evaluated in triplicate for *in vitro* drug release kinetics by using *USP* Type-II (paddle method) dissolution test apparatus (Electrolab, TDT 08L, Mumbai, Maharashtra, India). Dissolution medium used was hydrochloric acid buffer pH 1.2 *USP* (900 mL) for first 2 h, which was further replaced by phosphate buffer pH 6.8 *USP* (900 mL), both maintained at 37.5 ± 0.5 °C (Sahu, 2010; USPNF, 2006b). Paddle speed was set constant at 75 rpm (USPNF, 2011). At predetermined time intervals, aliquots of 5 mL were withdrawn and sink condition was maintained by replacing the withdrawn quantity with respective fresh dissolution media (37.5 ± 0.5 °C). By using Whatman cellulose filter paper no. 42 (retention of 2.5 μm particle size) collected aliquots were filtered and analyzed spectrophotometrically (Shimadzu Corporation, UV-1800, Japan) at 228 for pH 1.2 and 227 nm for pH 6.8 (Sahu, 2010).

2.2.3.7. In vitro drug transportability studies. *In vitro* drug transportability studies across dialysis membrane (HiMedia Laboratories Pvt. Ltd., Mumbai, Maharashtra, India) were performed for all batches (GMR1 to GMO3) in triplicate by using designed glass tube. Internal diameter of glass tube was 22 mm with an area of 314 mm^2 available for drug transport divided into a total of 25 orifices on the surface (each orifice with 4 mm internal diameter). Receiver compartment of tube measures volume (capacity) about 17 mL. Dialysis membrane was coiled around the external surface of the tube after soaking the membrane for overnight in respective dissolution/receptor media. The glass tube with coiled membrane around it was then introduced between the basket wall and the paddle shaft of dissolution test apparatus containing dissolution media maintained at 37.5 ± 0.5 °C. All other variables (dissolution medium, total time period, set of temperature conditions, paddle speed, sampling volume and time points) were kept constant as specified under *in vitro* dissolution study. Aliquots of 5 mL were taken at specified time intervals from receptor medium (volume = about 17 mL) and subsequently filtered using Whatman cellulose filter paper no. 42. The filtrates were then analyzed spectrophotometrically (Shimadzu Corporation, UV-1800, Japan) at observed λ_{max} and % drug transport was calculated. Withdrawn quantity of media was replaced with the same amount of respective fresh media maintained at identical temperature conditions.

2.2.4. QSPR model development

2.2.4.1. Calculation of descriptors. A builder module of the Vlife MDS 4.2 commercial software was used to draw the molecular models/structures of polymers. Further, Merck Molecular Force Field was used for energy optimization or minimization of the drawn structures until the value of root mean square gradient reaches to 0.001 kcal/mol Å. Subsequently, each polymeric structure was subjected for the calculation of several descriptors (⩾118) from diverse physicochemical sub-classes such as Chi, Chiv, Chi Chain, Chiv Chain, Chain Path count, Individual, Path Count, Cluster, Path Cluster, Kappa, Element Count, Electrostatic, Distance based Topological, Polar Surface Area, Hydrophobicity SlogpA, Hydrophobicity SlogpK, Hydrophobicity XlogpA and Hydrophobicity XlogpK. These sub-classes consist of several descriptors as representative of polymeric physicochemical properties that would serve as the measure of interactions between polymer and dissolution media along with other formulation components (drug and excipients).

2.2.4.2. Selection of molecular descriptors. Moreover, descriptors were selected by correlating dissolution data ($t_{90\%}$: time required for 90% release of initial drug amount), transportability data ($\%T_{60min}$: percent of drug amount transported at 60 min) and related formulation properties with calculated molecular descriptors (⩾118). Further invariable descriptors showing insignificant correlation with dependent variable were eliminated and a data set of 60 significant descriptors so obtained was again allowed for correlation analysis with the response. This resulted into an estimation of the correlation coefficient of individual descriptor and further assisted in selection of the best set of descriptors with the most significant correlation. At the end of the process a total of 5 molecular descriptors have been selected based on assessment of best correlation and considerable impact shown by individual descriptor on response under study.

2.2.4.3. Model development and validation for QSPR analysis. The data set was divided into the training and test set molecules after entering the percentage (70%) of training set molecules by using Random data selection method in Vlife MDS 4.2 commercial software. Further QSPR model was developed with the use of training set having known data of the response ($t_{90\%}$, $\%T_{60min}$ and related formulation properties). Predictability of developed QSPR model was then assessed by challenging the model against test set molecules (not included in model generation).

2.2.4.4. Multiple linear regression (MLR) analysis. Commonly, independent variables with significant impact were preferred in the model development process to yield most proficient and successful QSPR model. The practical use of the developed model is based on its ability for replicating any variation in polymeric design parameters on drug release or drug concentration profile (Siepmann and Siepmann, 2008; Siepmann et al., 2000). Hence, the present investigation was aimed to develop a highly predictive QSPR model through MLR analysis between 5 molecular descriptors (independent variables) and $t_{90\%}$, $\%T_{60min}$ and related formulation properties (dependent variables) by using a 2D QSAR tool of Vlife MDS 4.2 commercial software. Several combinations of training and test set molecules selected on random basis were tested to yield a top promising QSPR model. From randomly generated different QSPR models through MLR analysis, a set of top 3 physicochemical sub-classes of descriptors showing best correlation and significant effect on response have been identified. From these sub-classes, a set of not more than 5 descriptors as independent variables were randomly selected and processed through MLR analysis by user defined variable selection method for generation of at least 4 QSPR equations or regression models. Eventually from last 4 developed models, a QSPR model with least standard error and best correlation coefficient was selected. Therefore, without real formulation of a dosage form a QSPR model developed in such a way has good predictive potential for formulation composition

for required characteristics and hence could have a pharmacoeconomic impact on future research.

3. Results and discussion

The present study involves evaluation of GLMP (a model drug from neutral category) tablet formulations prepared using 3 polymers from 3 different categories (extended, moderate and immediate release). Then QSPR model was developed through correlation analysis between the generated experimental data and the molecular descriptors calculated for polymers. The developed model could have high predictability for characteristics of GLMP tablet formulations and also could promote future formulation design trials. Though the present study does not consider the modeling of parameters other than hardness, friability, drug release and transportability profiles, these other evaluated parameters could help to ensure the formation of tablets with acceptable characteristics exhibiting required rate of drug release under specified experimental conditions.

3.1. Characterization of drug and excipients

3.1.1. Standard curve

Detection of λ_{max} at 228 in hydrochloric acid buffer pH 1.2 *USP* and at 227 nm in phosphate buffer pH 6.8 *USP* confirmed GLMP molecule which is in good agreement with previous reports (Wagh et al., 2012; Sahu, 2010). A linear equation from calibration curve of GLMP indicated coefficient of correlation, slope and intercept as +0.9996, 0.0062 and +0.1 in buffer pH 1.2, however as +0.9992, 0.0663 and +0.013 in buffer pH 6.8, respectively.

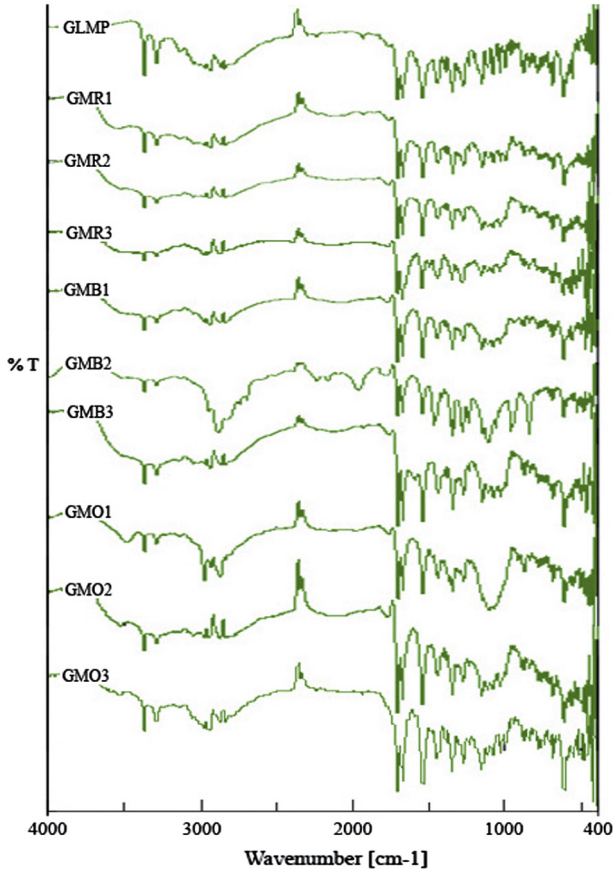

Figure 1 FTIR spectra of pure GLMP and tablet formulations (GMR1 to GMO3).

3.1.2. FTIR studies

Identification and confirmation of GLMP were done by observing characteristic peaks of pure GLMP in FTIR spectrum by using the KBr method (Fig. 1). Characteristic peaks in the FTIR spectrum of pure GLMP were observed at 3374.82 and 3287.07 (N—H stretching for urea); 2981.13 and 2937.06 (C—H); 1705.36, 1703.67 and 1601.19 (>C=O); 1674.76 (N—H bending); 1500–600 (C—H and =C—H bending); 1341.62 and 1155.23 (S=O stretching vibration in sulfonamide group); 1346.48, 1078.93 and 1039.13 (C—N stretching vibration). These peaks were identical with reported standard peaks confirming the molecule as 3-ethyl-2,5-dihydro-4-methyl-*N*-[2-[4-[[[[(*trans*-4-methylcyclohexyl)-amino]carbonyl] amino]sulfonyl]phenyl]ethyl] 2-oxo-1*H*-pyrrole-1-carboxamide (IP, 2010a; USPNF, 2006c; Moffat et al., 2004).

Furthermore, all tablet formulations (GMR1 to GMO3) have shown very less or negligible shifting of GLMP peaks as observed in the FTIR spectra (Fig. 1) indicating no any chemical or structural alteration in GLMP. Such a slight or minute shifting observed in peak intensity could be related to the polymer adsorption onto the surface of the drug. Therefore tablet formulations of GLMP with selected excipients can be prepared without losing its potency.

3.2. Evaluation of tablet formulations

Physical evaluation of all prepared tablet formulations (GMR1 to GMO3) indicated zero defects with smooth surface, odorless, flat in shape and white in color. Furthermore, evaluation of different post-compression parameters was completed as discussed below.

3.2.1. Weight uniformity

Uniformity of weight indicated the values between −0.85 ± 0.65% and 0.84 ± 0.49% deviation (Table 2) from an average weight of the tablets (400 ± 5 mg) for all formulations (GMR1 to GMO3). It has been observed that the deviation falls within the acceptable prescribed standards (±5% deviation approved for 250 mg or more average weight) indicating uniformity in tablet weight (IP, 2010b). This was associated with the free flowing property of granules, invariable die filling and compression of tablets with constant hardness.

3.2.2. Drug content

All formulation batches (GMR1 to GMO3) showed uniformity in content of GLMP ranging from 97.42 ± 3.67% to 104.86 ± 2.73% (Table 2) with adequate precision. The observed GLMP content was within the acceptable official standards which states that glimepiride tablets contain not less than 90.0% and not more than 110.0% of the stated amount of glimepiride, $C_{24}H_{34}N_4O_5S$ (IP, 2010a; USPNF, 2011).

3.2.3. Hardness

Hardness for all tablet formulations (GMR1 to GMO3) was observed within a narrow range of 4.20 ± 0.28 to

Table 2 Post-compression evaluation of GLMP compacts.[a]

Batch code	Weight uniformity (% deviation)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Diameter (mm)
GMR1	0.84 ± 0.49	101.87 ± 1.82	4.50 ± 0.10	0.242 ± 0.033	4.13 ± 0.012	10.05 ± 0.006
GMR2	0.45 ± 0.56	100.31 ± 3.23	4.67 ± 0.34	0.171 ± 0.027	4.13 ± 0.020	10.06 ± 0.005
GMR3	0.72 ± 0.55	104.86 ± 2.73	4.20 ± 0.28	0.303 ± 0.022	4.14 ± 0.015	10.05 ± 0.005
GMB1	0.52 ± 0.58	100.71 ± 4.60	4.51 ± 0.19	0.231 ± 0.014	4.14 ± 0.006	10.06 ± 0.010
GMB2	−0.56 ± 0.65	98.08 ± 4.26	4.65 ± 0.13	0.181 ± 0.021	4.13 ± 0.015	10.05 ± 0.012
GMB3	−0.23 ± 0.65	99.85 ± 1.73	4.77 ± 0.57	0.153 ± 0.012	4.12 ± 0.021	10.06 ± 0.017
GMO1	−0.04 ± 0.65	100.02 ± 5.96	4.70 ± 0.20	0.177 ± 0.019	4.13 ± 0.017	10.06 ± 0.012
GMO2	0.58 ± 0.64	101.82 ± 3.17	4.53 ± 0.21	0.217 ± 0.011	4.13 ± 0.006	10.06 ± 0.017
GMO3	−0.85 ± 0.65	97.42 ± 3.67	4.83 ± 0.23	0.122 ± 0.018	4.12 ± 0.015	10.06 ± 0.020

[a] Indicates average ± SD (n = 3).

4.83 ± 0.23 kg/cm^2 indicating uniformity in tablet hardness (Table 2). To withstand the mechanical shocks commonly observed during the machine operations, packaging and transportation, the tablets must be formulated with adequate hardness as indicative of tablet strength showing better handling characteristics. A tablet formulation with lowest hardness (batch GMR3) showed minimum $t_{90\%}$ attributed to the lesser densification associated with greater porosity that could have facilitated the entry of dissolution medium and accordingly faster drug release.

3.2.4. Friability

In the present study, an inverse relationship between hardness and friability of tablets has been observed where friability for all GLMP batches (GMR1 to GMO3) showed variation between 0.122 ± 0.018% and 0.303 ± 0.022% (Table 2). All tablet formulations pass the friability test as observed results were within the reported official standards [not more than 1%] (USPNF, 2006a). Friability data for all formulations (GMR1 to GMO3) were found to be in good agreement with *in vitro* drug release studies and hardness associated with improved handling characteristics.

3.2.5. Uniformity of thickness and diameter

Uniformity in thickness and diameter of tablets from all batches (GMR1 to GMO3) has been observed within a narrow range of 4.12 ± 0.015 to 4.14 ± 0.015 mm and 10.05 ± 0.005 to 10.06 ± 0.020 mm, respectively (Table 2). All observed results for tablet dimensions were within the acceptable limits (±5%) of tablet size.

3.2.6. In vitro drug release kinetics

Prepared GLMP compacts (GMR1 to GMO3) have been evaluated in triplicate for dissolution kinetics using *USP* Type-II (paddle method) dissolution test apparatus. Dissolution data obtained were further processed for estimation of the mechanism of drug release by linear regression analysis to test the goodness of fit for different kinetic models such as Zero order, First order, Hixson-crowell, Higuchi matrix or Korsmeyer-peppas kinetics. *In vitro* drug release profiles and kinetic parameters with regression data of GLMP tablet formulations were presented in Figs. 2 and 3 and Table 3, respectively.

Korsmeyer-peppas kinetic model was observed as the best fit for GMR1 to GMB2 formulations (r = 0.9756–0.9894),

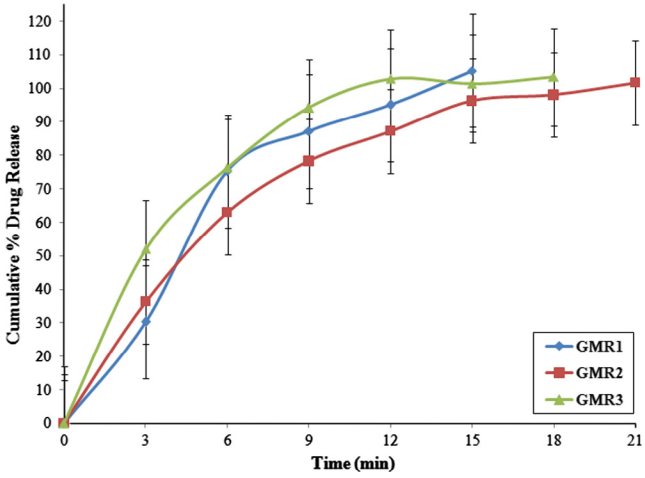

Figure 2 *In vitro* drug release kinetics from GMR1 to GMR3 formulations.

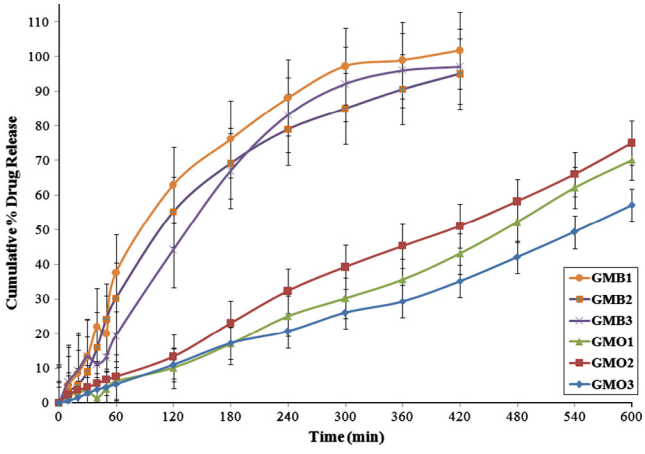

Figure 3 *In vitro* drug release kinetics from GMB1 to GMO3 formulations.

however batches GMB3 to GMO3 showed zero order kinetics (r = 0.9824–0.9991) as given in Table 3. Additionally, release exponent (n) indicated super case-II transport (n > 1.0) type of drug release mechanism from GMR1 to GMB2

Table 3 *In vitro* drug release and transportability kinetics from GLMP tablet formulations.

Batch code	Zero order model (r)[a]	First order model (r)[a]	Higuchi model (r)[a]	Hixson-crowell model (r)[a]	Korsmeyer-peppas model (r)[a]	Korsmeyer - peppas model (n)[a]	Best fit kinetic model	$t_{90\%}$ (min)	$\%T_{60min}$ (%)[b]
GMR1	0.9472	−0.9916	0.9486	−0.9335	0.9786	1.1991	Korsmeyer-peppas	10	23.02 ± 3.01
GMR2	0.9222	−0.9873	0.9753	−0.9602	0.9894	1.8225	Korsmeyer-peppas	12.8	15.95 ± 2.33
GMR3	0.8774	−0.9843	0.9609	−0.9577	0.9756	2.3468	Korsmeyer-peppas	8.2	43.01 ± 3.78
GMB1	0.9538	−0.9811	0.9817	−0.9719	0.9828	1.1434	Korsmeyer-peppas	251	24.18 ± 2.87
GMB2	0.9577	−0.9976	0.9757	−0.9947	0.9839	1.0095	Korsmeyer-peppas	353	14.31 ± 2.19
GMB3	0.9824	−0.9909	0.9769	−0.9947	0.9723	1.1458	Zero order	282	17.18 ± 1.85
GMO1	0.9955	−0.9706	0.9532	−0.9819	0.9652	0.9686	Zero order	799	5.87 ± 1.05
GMO2	0.9991	−0.9842	0.9736	−0.9932	0.9945	1.1156	Zero order	700	6.84 ± 1.62
GMO3	0.9972	−0.9839	0.9646	−0.9899	0.9961	0.9572	Zero order	834	2.89 ± 0.69

[a] Where 'r' and 'n' are coefficient of correlation and release exponent (Korsmeyer-peppas model), respectively.
[b] Indicates average ± SD (n = 3).

formulations [Table 3] (Siepmann and Siepmann, 2008; Costa and Lobo, 2001; Grassi and Grassi, 2005; Korsmeyer et al., 1983; Dash et al., 2010; Siepmann and Peppas, 2001). It has been reported that formulation following Korsmeyer-peppas kinetic is indicative of the involvement of more than one mechanism and/or unclear or unknown mechanism of drug release (Costa and Lobo, 2001).

It has been observed that the type of polymer incorporated has majorly contributed in deciding the rate of drug release in immediate release formulations (GMR1 to GMR3). Additionally, tablet hardness might have contributed in controlling $t_{90\%}$ to some extent (Tables 2 and 3) as observed with GMR3 where lowest $t_{90\%}$ (8.2 min) was associated with lower hardness of the tablet. This was attributed to the highly cross-linked structure of CPVP that allows entrapment of water molecules to higher extent causing faster swelling of the matrix with a net result of the faster GLMP release (Fig. 2). Conversely, higher $t_{90\%}$ (12.8 min) for batch GMR2 could be related to the comparative poor wettability of CCS taking the maximum time for tablet wetting together with reduced contact between drug and dissolution medium with the net result as a slower rate of drug release (Fig. 2). All immediate release batches (GMR1 to GMR3) followed Korsmeyer-peppas kinetics with super case-II transport (release exponent $n > 1.0$) type of mechanism for GLMP release.

Formulation GMB2 from moderate release category showed higher $t_{90\%}$ (353 min) indicative of GLMP release at slower rates (PEG 6000). Fig. 3 clearly illustrates the initial faster rate of GLMP release from batch GMB2, however, after 3 h a reduced rate of release has been observed attributed to the formation of local highly viscous polymeric layer (PEG 6000) around the tablet surface that limits the rate of drug diffusion in the dissolution medium. Batch GMB1 (ME15) showed faster drug release ($t_{90\%}$ = 251 min) than GMB2 and GMB3 (Table 3 and Fig. 3) attributed to the more hydrophilic nature of ME15. It has been observed that ME15 gets quickly hydrated with the formation of an outer gelatinous layer creating a barrier in further wetting of tablet core with the net result as reduced initial faster release rate (Fig. 3). After complete hydration, the formed gel layer gets dissolved into the medium with time which was replaced by inner continuous fresh gel layer that further slows down the entry of medium into the tablet core and allows drug release in a more controlled way (Gafourian et al., 2007). If polymer (ME15) is thermodynamically compatible with the dissolution medium it causes relaxation of polymeric chains upon contact with dissolution medium that subsequently increases chain flexibility with volume expansion. As a result faster rate of drug release out of polymeric matrix has been observed (Wu et al., 2005). Drug diffuses from ME15 matrix specifically through swelling, diffusion and erosion front formed as a result of contact with the dissolution medium (Siepmann and Peppas, 2001). Improvement in thickness of above 3 fronts with the time further leads to increased path length for drug diffusion with a net effect of reduced release rate for maximum time (Colombo et al., 2000, 1999). Moreover, tablet formulation GMB3 showed the initial slower rate of GLMP release attributed to comparative lower solubility of CMCS than GMB1 (ME15) and GMB2 (PEG 6000) that limits the availability of drug to dissolution medium (Fig. 3). Previous researchers have reported that drug release from any dissolvable polymer majorly occurs through either swelling or dissolution or combination of these two mechanisms (Tahara et al., 1995; Efentakis and Buckton, 2002). Formulations GMB1 and GMB2 indicated Korsmeyer-peppas model as best fit with super case-II transport (release exponent $n > 1.0$) mechanism for drug release, however batch GMB3 followed Zero order kinetics for release of GLMP from tablets (Table 3).

Among extended release formulations (GMO1 to GMO3), batch GMO3 (ERS100) exhibited maximum $t_{90\%}$ (834 min) indicating drug release for extended time (Table 3 and Fig. 3). This was attributed to pH independent swelling, insolubility and lower permeability of polymer for dissolution medium with a net effect of pH independent and time controlled GLMP release. The low permeability and insolubility of ERS100 was attributed to the presence of a limited number of ammonium groups or salts that restricts the formation of channels for entry of dissolution medium into the tablet core

plus drug diffusion outside the matrix. Next to batch GMO3, formulation GMO1 showed extended GLMP release ($t_{90\%}$ = 799 min) due to the highly hydrophobic nature of EC10 with negligible wetting ability. However, tablet formulation GMO2 containing HPC indicated comparatively faster rate of GLMP release ($t_{90\%}$ = 700 min) as shown in Fig. 3. All formulations from extended release category (GMO1 to GMO3) followed Zero order kinetics for release of GLMP from tablets.

3.2.7. *In vitro drug transportability studies*

While performing the dissolution study, all tablet formulations (batches GMR1 to GMO3) were simultaneously evaluated for transportability profiles in triplicate using glass tube specially designed for transportability studies. After applying dialysis membrane on the external surface, the glass tube was placed in a dissolution basket between the paddle shaft and wall of the basket. After the release and subsequent dissolution from tablet formulation, drug gets transported across the dialysis membrane into the receiver compartment of the tube. This approach results into simultaneous estimation of release and transportability profiles. The data obtained were further analyzed for estimation of percent amount of drug transported at 60 min from the plot of $\%T_{60\text{min}}$ against time. Evaluation parameters ($\%T_{60\text{min}}$) and transportability profiles for all tablet formulations (GMR1 to GMO3) were presented in Table 3 and Fig. 4, respectively.

Batches GMR1 to GMR3 (immediate release formulations) exhibited the release rate dependent transportability profiles where batch GMR3 (CPVP) showed a faster rate of drug transport ($\%T_{60\text{min}}$ = 43.01%, Table 3) due to the higher availability of dissolved drug (Figs. 2 and 4). This was attributed to the highly crosslinked structure of CPVP that allows entrapment of more amount of water with the net result as higher chain relaxation with faster disintegration and drug release. However, too high quantity of drug available for transport at once could also result in steady or constant transportability profile due to the membrane pore sealing effect.

Tablet formulations with moderate drug release profiles (batches GMB1 to GMB3) showed a gradual increase in the transport rate of GLMP (Fig. 4). A comparative lower availability of drug released in dissolution media for transport across membrane resulted into faster rates of transport. Batch GMB1 exhibited a faster transport of GLMP ($\%T_{60\text{min}}$ = 24.18%, Table 3) due to the hydrophilic nature of ME15 having more affinity for dissolution medium that increases the thermodynamic activity of the drug in the membrane with a net effect as increased drug release. Moreover, the higher p*K*a (6.2 at 25 °C) and lower water solubility (0.004 mg/mL) of GLMP could result in retention of GLMP in more unionized form that gets across the membrane more easily and hence faster rate of drug transport (Table 3).

Extended release formulations (GMO1 to GMO3) also showed rate of GLMP transport depends on the release profile. The release of drug for extended time causes limited availability of drug for transport than membrane area and hence results into a complete and fast transport of available quantity as indicated by higher relative rate of transport compared to release (Figs. 3 and 4). Formulation GMO3 (ERS100) exhibited slower rate of drug transport ($\%T_{60\text{min}}$ = 2.89%, Table 3) than GMO1 and GMO2 (Fig. 4) due to the time controlled release based on the concentration used in the formulation. Moreover, batch GMO1 (EC10) also showed transportability profile matching with batch GMO3. This was attributed to the highly hydrophobic nature of EC10 with less affinity for water or dissolution media with a net result of thermodynamically reduced activity of the drug in the membrane. This resulted in the reduced release and transport of drug across the membrane. A slower rate of drug release from extended compared to immediate and moderate release formulations limits the availability of drug for transport and that would not cease the membrane pores. This resulted in the increased rate of transport relative to the release rate of the drug from matrices indicating the influence of some other factors related to the drug such as log *P* on transportability profile.

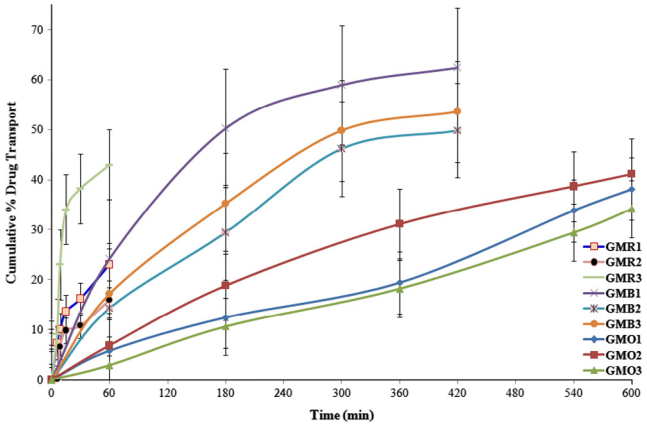

Figure 4 *In vitro* transportability profiles from GMR1 to GMO3 formulations.

3.3. *QSPR model development*

Statistical or mathematical models have been developed with an ability to quantify the drug release kinetics, transportability profile and related formulation properties from pharmaceutical products. QSPR model is selected on the basis of its accuracy and predictive ability for early estimation of response under investigation, which could be helpful in the development of new drug delivery systems (Siepmann and Peppas, 2001). Consequently, developed models must be highly realistic way with lower complexity issue for a number of variables considered in the model development process. Process for the development of new model must be associated with comparison of theoretical calculations with the observed results. However, the limited applicability of developed models in the design of different formulation systems could be related to the complexity of models and ultimately on a number of variables considered (Siepmann and Siepmann, 2008).

Molecular models of polymers were drawn and energy minimized by using Vlife MDS 4.2 commercial software. Subsequently, a number of molecular descriptors ($\geqslant$118) were calculated for each polymeric structure and correlated with formulation properties for selecting a set of descriptors with good correlation. Development and validation of models were completed by dividing the descriptors into training and test set molecules. Ultimately, a set of not more than 5 best descriptors

Table 4 Regression analysis data from QSPR modeling of GLMP formulations.[a]

Sr. No.	Name of parameter	Regression coefficient (relative coefficient)			
		Hardness	Friability	$t_{90\%}$	$\%T_{60min}$
1.	r^2	0.8981	0.9761	0.9741	0.8761
2.	q^2	0.4647	0.7017	0.7483	0.4134
3.	*F*-statistic	5.2874 (analysis is significant)	24.4556 (analysis is significant)	22.5723 (analysis is significant)	4.2437 (analysis is significant)
4.	Standard error	±0.0979	±0.0136	±89.0035	±7.0358
5.	Intercept	+5.058	+0.149	−285.711	+65.870
6.	XAAverage Hydrophilicity	+4.674 (+0.9661)	–	−53.268 (−0.0259)	–
7.	VolumeCount	+0.032 (+0.0066)	–	–	–
8.	SAMostHydrophobic Hydrophilic Distance	+0.004 (+0.0008)	+0.005 (+0.0420)	–	−0.992 (−0.0864)
9.	chiV4	−0.108 (−0.0223)	–	–	–
10.	kappa3	−0.020 (−0.0041)	+0.005 (+0.0420)	–	–
11.	H-AcceptorCount	–	−0.052 (−0.4369)	–	–
12.	slogp	–	−0.041 (−0.3445)	–	–
13.	chi0	–	+0.016 (+0.1345)	–	–
14.	H-DonorCount	–	–	−28.063 (−0.0137)	–
15.	XKMostHydrophobic	–	–	+1727.322 (+0.8417)	–
16.	XKMostHydrophobicHydrophilicDistance	–	–	+35.483 (+0.0173)	–
17.	BalabanIndexJ	–	–	+207.962 (+0.1013)	−8.199 (−0.7141)
18.	smr	–	–	–	+0.217 (+0.0189)
19.	kappa2	–	–	–	(−2.024 (−0.1763)
20.	XAHydrophobicArea	–	–	–	(−0.050 (−0.0044)

[a] Where r^2 is calculated squared correlation coefficient and q^2 is predicted correlation coefficient (at $p < 0.05$).

was selected as independent variables for MLR analysis against response variable ($t_{90\%}$, $\%T_{60min}$ and related formulation properties). This resulted in the generation of a QSPR model exhibiting high coefficient of determination and minimum standard error with potential predictability (Table 4).

3.3.1. Hardness

'XAAverageHydrophilicity' showed highest positive effect on tablet hardness (relative coefficient = +0.9661, Table 4). 'XAAverageHydrophilicity' descriptor signifies average hydrophilic value on the vdW surface. This parameter would enhance bonding of water with the binder polymer and other excipients and hence the presence of a polymer having high hydrophilic count on the vdW surface causes formation of harder tablet with a net result of delayed disintegration of the tablet and slower initial drug release.

'VolumeCount' descriptor also exhibited significant positive impact on hardness (relative coefficient = +0.0066, Table 4). 'VolumeCount' descriptor signifies volume of a compound. This indicates the increased tablet hardness with incorporation of a polymer having high volume related to higher compressibility and improved physical bonding with other molecules that result in the formation of harder tablet.

Another descriptor 'SAMostHydrophobicHydrophilicDistance' exhibited least positive effect on tablet hardness (relative coefficient = +0.0008, Table 4). 'SAMostHydrophobicHydrophilic-Distance' descriptor signifies distance between most hydrophobic and hydrophilic point on the vdW surface that indicates the net polarity index on polymer surface. The positive coefficient of regression indicates increased distance between two points with the reduction in net polarity that leads to the formation of harder tablet.

However, 'chiV4' showed a considerable negative impact on tablet hardness (relative coefficient = −0.0223, Table 4) indicating decreased hardness/strength of the tablet in the presence of a polymer having high 'chiV4' property. 'chiV4' descriptor signifies the atomic valence connectivity index (order 4). Thus, multiple connectivity or branched polymeric matrix would lead to a decrease in hardness and this influence of the 'chiV4' descriptor is in agreement with the well accepted and reported influence of branched polymers on tablet hardness.

Another descriptor 'kappa3' also exhibited negative impact on hardness (relative coefficient = −0.0041, Table 4) as indicative of reduced hardness with increase in shape index. 'kappa3' descriptor signifies the third kappa shape index. Higher index denotes more uniform particles with the poor physical bonding that leads to reduction in hardness or strength of the tablet.

3.3.1.1. QSPR equation. A set of maximum 5 descriptors (explanatory variables) based on their good correlation and significant impact on hardness (dependent variable) was selected for generation of numerous QSPR models. Further, a model exhibiting best correlation and minimal standard error was selected for predicting tablet hardness (Eq. (2)).

$$\begin{aligned}\text{Hardness} = {} & +4.674 \times \text{XAAverageHydrophilicity} + 0.032 \\ & \times \text{VolumeCount} - 0.108 \times \textit{chiV}4 - 0.020 \\ & \times \text{kappa3} + 0.004 \\ & \times \text{SAMostHydrophobicHydrophilicDistance} \\ & + 5.058\ (\pm 0.0979) \end{aligned} \quad (2)$$

Eq. (2) shows a statistical model developed for hardness indicating significant correlation between all 5 descriptors and hardness of GLMP tablets ($r^2 = 0.8981$) with lowest standard error (± 0.0979) and mean response as $+5.058$ as shown in Table 4. All independent variables have shown significant impact over tablet hardness as indicated by *F*-test (5.2874). From squared correlation coefficient, 89.81% of the change in tablet hardness can be elucidated by the change in the 5 independent descriptors. Hence, hardness of tablet could be significantly predicted from polymeric properties by using the developed model (Eq. (2)).

3.3.2. Friability

'H-AcceptorCount' showed a significant negative impact on tablet friability (relative coefficient = −0.4369, Table 4) indicating reduced friability with the incorporation of a polymer having a high H-bond accepting ability. 'H-AcceptorCount' represents the number of hydrogen bond acceptor atoms. High H-bond acceptor count is associated with improved physical bonding with active pharmaceutical ingredient (API) that results in increased hardness and reduced friability of the tablet.

Another descriptor 'slogp' also exhibited negative impact on tablet friability (relative coefficient = −0.3445, Table 4). 'slogp' descriptor signifies log of the octanol/water partition coefficient. The inverse relationship is indicative of the formation of harder tablet having lower friability with reduction in polarity or the increase in hydrophobicity of polymers.

However, 'kappa3' and 'SAMostHydrophobicHydrophilic Distance' both have indicated positive and equal impact on tablet friability (relative coefficient = +0.0420, Table 4). 'kappa3' descriptor signifies third kappa shape index and 'S AMostHydrophobicHydrophilicDistance' descriptor signifies the distance between most hydrophobic and hydrophilic points on the vdW surface. Higher values of shape index descriptor indicate increased regularity in particle shape, which further decreases particle initial adjustment during compression, and results into the formation of tablet with lower hardness or greater friability. Similarly, increased distance between most hydrophilic and hydrophobic points on the vdW surface ('SAMostHydrophobic-HydrophilicDistance') also resulted in increased tablet friability.

Another descriptor 'chi0' also showed the highest positive impact on friability (relative coefficient = +0.1345, Table 4). 'chi0' descriptor signifies a retention index (zero order) derived directly from gradient retention times. Increased friability has been observed due to increase in retention index, which is also a measure of relative hydrophobicity.

3.3.2.1. QSPR equation. Several QSPR models for predicting tablet friability have been developed by selecting not more than 5 descriptors (independent variables) based on their high correlation and considerable effect over friability (response variable). Ultimately, a model with high coefficient and smallest standard error was selected as given in Eq. (3).

$$\begin{aligned}\text{Friability} = {} & -0.052 \times \text{H\_AcceptorCount} - 0.041 \times \text{slogp} \\ & + 0.005 \times \text{kappa3} + 0.016 \times \textit{chi0} + 0.005 \\ & \times \text{SAMostHydrophobicHydrophilicDistance} \\ & + 0.149(\pm 0.0136) \end{aligned} \quad (3)$$

Statistical model developed for tablet friability (Eq. (3)) indicated a good correlation with all 5 polymeric properties ($r^2 = 0.9761$) with mean response as +0.149 and standard error as ±0.0136 (Table 4). A significant effect of all independent variables on friability was indicated by *F*-statistics (24.4556). From model 97.61% of the change in friability can be described by the change in 5 explanatory variables. Hence, developed model (Eq. (3)) can be used to study the effect of individual variable over response as well as for quantitative prediction ($q^2 = 0.7017$) of tablet friability based on the calculated polymeric properties.

3.3.3. In vitro drug release profile

'H-DonorCount' showed a significant negative impact on $t_{90\%}$ of GLMP (relative coefficient = −0.0137, Table 4) indicating faster rate of drug release. 'H-DonorCount' represents the number of hydrogen bond donor atoms (—OH and >NH) in structure. Polymer with highest H-bond donor count allows the formation of H-bonding with water molecules or dissolution media that releases the drug at a faster rate as observed with hydrophilic polymer. The faster release rate was attributed to the improved polymer wetting and availability of the drug to the dissolution media. Further, from dissolution profile drug gets released in the controlled manner attributed to the polymer and dissolution medium both competing simultaneously for the drug. The initial slower rate of drug release was related to the H-bonding formed with polymer (good 'H-DonorCount') present in the close vicinity of drug at a higher concentration than dissolution medium. Therefore, 'H-DonorCount' must be greatly considered for selection of a polymer in designing a drug delivery system for desired dissolution profile.

Another descriptor 'XAAverageHydrophilicity' exhibited highest negative impact on rate of GLMP release (relative coefficient = −0.0259, Table 4) indicating release of drug at a faster rate in the presence of a polymer having high hydrophilic value. 'XAAverageHydrophilicity' descriptor represents an average hydrophilic value on the vdW surface. A polymer having high hydrophilic character allows faster wetting and makes drug easily available to medium for dissolution. Hence, accelerated rate of drug release from formulation system containing polymer with high hydrophilic property has been observed.

However, 'XKMostHydrophobic' showed the highest positive impact on $t_{90\%}$ of GLMP (relative coefficient = +0.8417, Table 4) indicating a slower rate of drug release in the presence of a polymer having high hydrophobic character. 'XKMostH ydrophobic' descriptor signifies most hydrophobic value on the vdW surface. Polymer with higher hydrophobic value shows limited wetting and hence avoids further entry of dissolution media associated with decreased rates of drug release.

Moreover, 'XKMostHydrophobicHydrophilicDistance' descriptor also exhibited significant positive impact on GLMP release rate (relative coefficient = +0.0173, Table 4) signifying inverse relationship between rate of drug release and hydrophobic character reflected by the distance between most hydrophobic and hydrophilic points on polymer surface. 'XKMostHydrophobicHydrophilicDistance' descriptor signifies the distance between most hydrophobic and hydrophilic points on the vdW surface. Polymer with greater distance between two points is indicative of reduced polarity and hence

improved hydrophobic value. Accordingly reduced rate of drug release associated with limited wetting of the polymer has been observed.

Another descriptor 'BalabanIndexJ' also showed significant positive impact over $t_{90\%}$ of GLMP (relative coefficient = +0.1013, Table 4) as indicative of drug release at a slower rate. 'BalabanIndexJ' is a distance based topological descriptor represented by Eq. (4),

$$J = (E/\mu + 1)\sum(ds_i, ds_j) \quad (4)$$

where E is the number of edges, μ is the number of rings in a molecule, and ds_i, ds_j is sum of the row i and j of the distance matrix. This descriptor may be influencing the release profile due to the extent of the complementary shapes of the hydrophobic and hydrophilic surfaces of the polymer under study with respect to those of the API. This parameter would thus influence accessibility of the solubilizing media to the API which would be competing with the extent and strength of intermolecular interactions between the polymer and the API.

3.3.3.1. QSPR equation. A data set containing a maximum of 5 descriptors as independent variables based on the good correlation and significant effect over $t_{90\%}$ of GLMP (response variable) was selected for the development of a several models for predicting dissolution profile. A model with high squared correlation coefficient and low standard error was further selected (Eq. (5)).

$$\begin{aligned} t_{90\%} = {} & -28.063 \times \text{H-DonorCount} - 53.268 \\ & \times \text{XAAverageHydrophilicity} + 1727.322 \\ & \times \text{XKMostHydrophobic} + 207.962 \times \text{BalabanIndexJ} \\ & + 35.483 \times \text{XKMostHydrophobicHydrophilicDistance} \\ & - 285.711\ (\pm 89.0035) \end{aligned} \quad (5)$$

Eq. (5) and Table 4 give a set of polymeric descriptors that have contributed significantly in determining the GLMP release profiles from tablet formulations (batch GMR1 to GMO3). Coefficient of determination (r^2 = 0.9741, Table 4) indicated a very good correlation between all selected descriptors and $t_{90\%}$ of GLMP formulations. Therefore, 97.41% of the change in $t_{90\%}$ can be explained by the change in the 5 explanatory descriptors. The developed QSPR model showed overall mean response or intercept as −285.711 and minimal standard error (±89.0035). Also, predicted coefficient (q^2 = 0.7483, Table 4) reflects the considerable predictability of the model. *F*-statistics (22.5723) represented the significant effect of all 5 descriptors on $t_{90\%}$ (Table 4). Hence, developed model (Eq. (5)) could be used to predict the $t_{90\%}$ of any neutral drug based on the physicochemical properties of polymer integrated in formulation system. The predicted values are in good agreement with observed values for $t_{90\%}$ in developed QSPR model as shown in a plot of actual and predicted values (Fig. 5). Additionally, the theoretical prediction of the formulation composition for required release profile of other neutral drugs with acceptable precision could also be possible.

3.3.4. In vitro drug transportability profile

'Smr' showed the highest positive impact on $\%T_{60\text{min}}$ (relative coefficient = +0.0189, Table 4). 'Smr' descriptor evaluates molecular refractivity (including implicit hydrogens) which is also a measure of molecular size and also is an atomic contribution model that assumes the correct protonation state (washed structures). Thus, this composite of properties, which could be a measure of size as well as some types of non-bonded interactions that the polymer would have with the drug as well as the transport barrier, would evidently influence drug transport.

However, 'BalabanIndexJ' showed the highest negative impact on $\%T_{60\text{min}}$ (relative coefficient = −0.7141, Table 4) indicating reduced rate of drug transport in the presence of a polymer having high 'BalabanIndexJ'. 'BalabanIndexJ' is a distance based topological descriptors calculated by using Eq. (4). The negative value of its coefficient indicates reduced transport of drug with an increase in the value of this descriptor which is a measure of irregularity in shape of molecules of the polymer which would directly influence with the drug and the transport barrier. Alternatively the negative correlation to transportability could mean that the increase in the shape irregularity leads to increased interaction of the drug with the polymer and hence limits the transport of the drug.

Another descriptor 'kappa2' also showed significant negative impact over $\%T_{60\text{min}}$ (relative coefficient = −0.1763, Table 4). 'kappa2' descriptor signifies the second kappa shape index: $[(n-1)^2/m^2]$. The negative coefficient relates decreased rate of drug transport with an increase in the shape index/irregularity of polymeric particles that makes limited availability of drug for dissolution and subsequent transport across the membrane which is in good agreement with the reported common theory together with previous results reported under dissolution kinetics. 'kappa2' has also been a shape index and the influence of this descriptor on the transportability is found to be qualitatively similar to that of 'BalabanIndexJ' but both would serve as measures for different domains accounting for shape. Increased interaction of the polymer with the drug or decreased positive influence on the increase in transportability of the drug through the interaction of the polymer with the barrier may together be responsible for the negative contribution of this descriptor to transportability.

Moreover, 'SAMostHydrophobicHydrophilicDistance' descriptor also exhibited significant negative impact over $\%T_{60\text{min}}$ (relative coefficient = −0.0864, Table 4). 'SAMostHydrophobic-HydrophilicDistance' descriptor signifies the distance between most hydrophobic and hydrophilic points on the vdW surface (by Audry method using Slogp). The negative coefficient indicates reduced transport of drug in the presence of polymer with larger distances separating the most hydrophobic and hydrophilic points on the VdW surface i.e. reduction in net polarity index of the polymer. This was accompanied by improved binding of drug with a complementary charge area over the surface of the polymer. This indicates limited interactions of small polar water molecules per unit surface area of polymer and hence results into longer wetting time with slower rate of drug release and ultimately a reduction in drug transport.

Moreover, 'XAHydrophobicArea' indicated least negative impact over $\%T_{60\text{min}}$ (relative coefficient = −0.0044, Table 4) signifying reduced rate of GLMP transport in the presence of a polymer having high hydrophobic surface area. 'XAHydrophobicArea' is a vdW surface descriptor showing the hydrophobic surface area (by Audry method using Xlogp). Polymer with highly hydrophobic surface area allows limited contact with dissolution medium and hence wetting

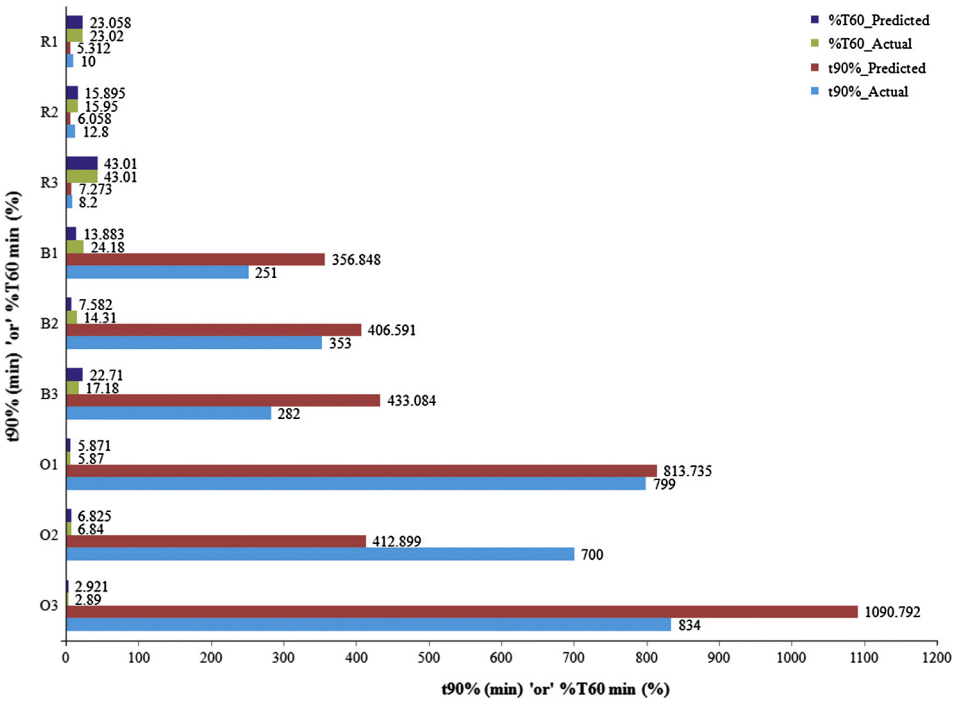

Figure 5 Actual and predicted values for $t_{90\%}$ and $\%T_{60\text{min}}$ of GLMP tablet formulations.

with drug release for an extended period of time. This limits the availability of drug amount for transport with the net result as reduced rates of transport which is in good agreement with results observed for *in vitro* dissolution kinetics.

3.3.4.1. QSPR equation. Minimum of 4 QSPR models for predicting transportability profile was generated by MLR analysis of different sets of descriptors as independent variables and $\%T_{60\text{min}}$ as the dependent variable. From this, a model with high correlation and low standard error was selected (Eq. (6)).

$$\begin{aligned}\%T_{60\text{min}} = {} & +0.217 \times \text{Smr} \\ & - 0.992 \times \text{SAM ostHydrophobicHydrophilicDistance} \\ & - 2.024 \times \text{kappa2} - 8.199 \times \text{BalabanIndexJ} - 0.050 \\ & \times \text{XAHydrophobicArea} + 65.870(\pm 7.0358) \qquad (6)\end{aligned}$$

QSPR model developed (Eq. (6)) indicated a good correlation ($r^2 = 0.8761$) between polymeric properties and $\%T_{60\text{min}}$ with lowest standard error (± 7.0358) and overall mean response as $+65.870$. By using developed model 87.61% of the change in $\%T_{60\text{min}}$ can be described by the change in the 5 descriptors. Moreover, developed model has considerable predictability for $\%T_{60\text{min}}$ as indicated by predicted coefficient ($q^2 = 0.4134$, Table 4). A significant effect of selected polymeric descriptors on response was indicated by *F*-statistics (coefficient = 4.2437, Table 4).

QSPR models developed in such a way on the basis of a comprehensive study of polymeric properties could help in the quantitative prediction of the transportability profile of any neutral drug. Fig. 5 represents a plot of actual and predicted values for $\%T_{60\text{min}}$ indicating a good agreement for $\%T_{60\text{min}}$ in the developed QSPR model. Such models could also assist in the early prediction of the formulation composition for a desired transportability profile.

4. Conclusion

Developed QSPR models can be used for predicting the release, transportability and other related formulation properties based on polymeric properties to be used in the unformulated dosage form. Furthermore, predicting formulation properties from other polymers exhibiting identical physicochemical properties could also be a possible outcome. Such several serial investigations which are currently in progress may lead to generation of models for predicting the composition of the formulation with required characteristics for each chemical class of drugs. This approach would positively affect the development of new formulation systems or optimization of the existing one without expensive and time-consuming testing in industrial research. Therefore, computer simulated QSPR models would become integral part of future formulation design trials in the pharmaceutical sector.

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