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Der Pharmacia Lettre, 2013, 5 (3):140-147
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Effect of polymeric properties on physical characteristics of fast disintegrating ibuprofen tablets: A statistical approach

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ABSTRACT

Present research was an attempt to develop a statistical relationship between physicochemical properties of polymers and physical characteristics of fast disintegrating tablets of ibuprofen. Polymers are generally used in formulation to provide effective drug delivery give as well as good physical appearance. Here, several physicochemical properties of three different polymers were calculated and correlated with formulation characteristics of ibuprofen tablets. Further, a statistical model with good correlation coefficient was used to explain the effect of different properties of polymers on evaluation parameters of tablets. Compatibility between ibuprofen and different polymers was confirmed through Fourier transform infrared spectroscopy analysis. All evaluated parameters for tablets such as weight uniformity (0.21± 0.33 to 0.52 ± 0.42 %), drug conte nt (98.12 ± 1.97 to 101.32 ± 2.24 %), hardness (4.30 ± 0.05 to 4.42 ± 0.06 Kg/cm^2) and friability (0.157 ± 0.035 to 0.323 ± 0.032 %) were found to comply with official limits. Developed statistical models for tablet hardness (correlation coefficient: r^2= +0.9597), friability (r^2= +0.9480) and disintegration time (r^2= +0.9989) indicated a good correlation between response under study and different physicochemical properties of polymers with significant analysis (F-test). Developed statistical models could have an ability to suggest the top physicochemical properties that need to be highly considered in selection of polymers for formulation with desired quality attributes. Additionally, such approach could be able to predict the formulation composition in advance and hence save time, material and formulation cost.

Keywords: Statistical model, Polymer, Ibuprofen, Disintegration time, physical properties.

INTRODUCTION

For effective delivery of drug to the desired site of action, drug need to be formulated into suitable dosage form. Additionally, a formulation with good physical strength is needed to withstand the mechanical shocks during handling and shipment. All these problems can be successfully overcome by incorporation of suitable polymeric excipients into the formulation. Therefore, selection of suitable polymer composite is the most important prerequisite in designing a formulation with desired characteristics. This would not be achieved without proper or extensive knowledge of physicochemical properties of polymers. Such polymeric properties representing the structure of polymer need not to be estimated experimentally but can be calculated theoretically with use of commercial software application. It has been reported that these properties tend to decide the wettability and disintegration of drug from its dosage form [1,2]. Therefore selection of polymer/s based on study of properties by computational analysis would contribute efficiently in deciding a formulation composition with desired quality attributes. A statistical relationship would suggest the best suited polymeric system for formulation as polymeric properties are likely to have significant relation with hardness and disintegration of tablets. Statistical or quantitative structure-property relationship (QSPR) modeling calculates the molecular descriptors representing the

physicochemical properties based on the information contained in structure of polymer [1,2]. Subsequently it correlates the calculated properties with property under examination to develop a mathematical model with high predictability for deciding a formulation composition through selection of best suited polymer or polymer composite. Such approach will have a very good impact on upcoming formulation development work through saving of material, time and formulation cost of pharmaceutical industry.

Therefore, present research was aimed to develop a statistical model with good predictability for selection of polymer/s in formulation design by correlating several physicochemical properties of different polymers with physical characteristics of formulation. This was accomplished by selecting three different polymers from cellulose semi-synthetic and synthetic class. Ibuprofen (IBP) was selected as a model drug representing acidic category. Total of three tablet formulations have been prepared and characterized for different post-compression parameters.

MATERIALS AND METHODS

Materials

IBP was kindly supplied by NuLife Pharmaceuticals (Pune, Maharashtra, India) as gift sample. Croscarmellose sodium (CCS, S.D. Fine-Chem Ltd., Mumbai, Maharashtra, India); Crospovidone (CPVP, S.D. Fine-Chem Ltd., Mumbai, Maharashtra, India) and Sodium starch glycolate (SSG, S.D. Fine-Chem Ltd., Mumbai, Maharashtra, India) were purchased. Starch, lactose, fumed silica and magnesium stearate were purchased from Research Lab, Mumbai, Maharashtra, India. All other ingredients used in study were of analytical grade.

Methods

Compatibility between Drug and Excipients

Identification of IBP and Standard Curve

Solution of pure drug (IBP) was scanned within range of 200 to 400 nm for identification using UV-Visible spectrophotometry (Shimadzu Corporation, UV-1800, Japan). Serial dilutions from stock solution of IBP in hydrochloric acid buffer pH 1.2 *USP (United States Pharmacopoeia)* [3] were made and analysed at observed λ_{max} for preparation of standard curve [4].

Fourier Transform Infrared Spectroscopy Analysis (FTIR)

FTIR analysis of pure drug (IBP) and tablet formulations (F1 to F3) was done to check the compatibility between IBP and excipients using KBr method by Jasco FTIR-4100 recording spectrometer within scanning range of 400 to 4000 cm^{-1} and the resolution at 1 cm^{-1} [4].

Formulation of Tablets

As per composition given in Table 1, a total of three batches (F1 to F3) of granules containing IBP were prepared by wet granulation technique. For this all powder ingredients were first obtained in uniform particle size by screening through mesh size 180 microns and then distilled water was added as granulating agent to obtain powder wet mass. This wet mass was converted into granules with uniform size by screening through mesh size 850 microns and then dried for 1 hour at 60 °C using hot air oven (Bio Technics India, Mumbai, Maharashtra, India). After drying, the granules were once more screened for uniform size using mesh size 600 microns. Further magnesium stearate as lubricant and fumed silica or aerosil as glidant were added to final mass of dried granules. Dried granules (600±5 mg) were then compressed into tablets for 4 – 5 Kg/cm^2 constant hardness by using 8-punch rotary tablet press (CIP Machineries Pvt. Ltd., Ahmedabad, Gujrat, India) with a set of die and 12-mm round flat-faced punch. After compression, the tablets were allowed to hardening and elastic recovery by keeping at ambient conditions for 24 hours [5]. Tablets so prepared were evaluated for numerous post-compression parameters: drug content, weight uniformity, hardness, friability, thickness, diameter and *in vitro* disintegration time (DT).

Table 1: Composition of IBP tablet formulations*.

Ingredients	F1	F2	F3
IBP	200	200	200
SSG	300	-	-
CCS	-	300	-
CPVP	-	-	300
Aerosil	13	13	13
Magnesium Stearate	25	25	25
Lactose	27	27	27
Starch	35	35	35
Total weight of compact (mg)	600 ± 5	600 ± 5	600 ± 5

**All quantities of ingredients are given in mg.*

Characterization of Tablet Formulations

Uniformity of Weight

From each batch (F1 to F3) randomly total 20 tablets were selected and by using electronic balance (Shimadzu AUX220) individual tablet weight was taken. Further % deviation of individual weight from average weight was calculated. As per official limits not more than two of the individual tablet weights should deviate from the average weight by more than ± 5% (for 250 mg or more) to pass the uniformity of weight test [6-8].

Drug Content

Drug content of from each batch (F1 to F3) was determined by powdering the pre-weighed sample of at least 10 tablets in glass mortar and pestle. Further accurately weigh the powder equivalent to 200 mg of ibuprofen and dissolve in 100 mL of phosphate buffer pH 6.8 *USP*. Resulting solution was suitably diluted, filtered and analyzed spectrophotometrically (Shimadzu Corporation, UV-1800, Japan) at 221 nm using phosphate buffer pH 6.8 *USP* as a blank [9]. By using standard curve, ibuprofen content of tablets was calculated. Each batch was evaluated in triplicate (n = 3) for estimation of drug content.

Hardness

Hardness of at least 3 tablets from each batch (F1 to F3) was determined using Monsanto-type hardness tester (Lab Hosp Corporation, Mumbai, Maharashtra, India). The indicator scale was set to zero after placing the tablet diametrically between the fixed and mobile surface of the tester. Then the force required (tablet hardness) to break the tablet was measured in Kg/cm^2 [8].

Friability

Friability of tablets from each batch (F1 to F3) was evaluated in triplicate (n = 3) using Roche friabilator (Electrolab, Mumbai, Maharashtra, India). Randomly selected 10 tablets were weighed and placed in plastic chamber revolving at 25 rpm for total of 100 revolutions allowing tablet drop across 6 inches height per revolution subjected to combined effect of shock and abrasion *(USP)* [10]. Subsequent to 100 revolutions tablets were removed from plastic chamber, dedusted and reweighed for calculation of percentage friability (F) by using equation 1 [8],

$$F = \frac{W_i - W_f}{W_i} \times 100 \qquad \text{..... 1}$$

Where, W_i and W_f are initial and final weights of tablets.

Tablet Dimensions

Uniformity in tablet dimensions was evaluated for at least 3 tablets from each batch (F1 to F3) by measuring the crown-to-crown thickness and diameter at 3 different points of each tablet using digital vernier calliper. The permitted limits for diameter and thickness are ± 5% of the tablet size.

In vitro DT

In vitro DT for 6 tablets from each batch (F1 to F3) was determined by inserting disks after placing one tablet in each tube in disintegration tester *USP* (Electrolab, ED-2L, Mumbai, Maharashtra, India). Immersion fluid used was 900 ml of distilled water maintained at 37 ± 2ºC. The time (seconds) required for the complete disintegration of the tablet together with no sign of palpable mass in the tube was recorded as DT. The test was performed in triplicate for each batch (n=3) [11].

Development of a Statistical Model

Descriptors representing structures of polymers were calculated by drawing molecular models in Vlife Molecular Design Suite (MDS) 4.2 and subsequently energy minimized using the Merck Molecular Force Field. A total of more than 100 physicochemical descriptors of each polymeric structure were calculated representing different physicochemical sub-classes. Moreover, a set of descriptors was selected on basis of best correlation observed between calculated descriptors and various physical characteristics of IBP tablet formulations. Subsequently, descriptors showing significant effect (more than 50 descriptors) were selected for further correlation analysis by calculating the correlation coefficient for each descriptor with response variable. Ultimately, a set of descriptors showing best correlation and considerable impact on property under investigation was selected for model development. Further, by using random data selection method various statistical models were developed through use of training set molecules having known data of response variable. Subsequently, the predictability of developed models was tested against the test set molecules, which was not included in model development process. Form above data, different sets of independent variables (a set of 5 descriptors) were selected and processed by multiple linear regression (MLR) analysis against one response variable (for e.g. hardness) by using user defined variable

selection method in Vlife MDS 4.2 commercial software to yield several (at least 4) models. Ultimately, a model with best correlation coefficient and minimum standard error was selected to study the effect of independent variables (polymeric properties, Table 2) on response variables (physical parameters of tablets) such as hardness, friability and DT. Mathematical models so developed could have an ability for early prediction of best suited polymer system and hence, formulation composition for desired characteristics.

Table 2: Physicochemical descriptors selected for model development

Sr. No.	Name of descriptor	Description
1.	H-Acceptor Count	Number of hydrogen bond acceptor atoms
2.	H-Donor Count	Number of hydrogen bond donor atoms
3.	SA Hydrophobic Area	vdW surface descriptor showing hydrophobic surface area (by Audry method using Slogp)
4.	XA Most Hydrophobic Hydrophilic Distance	Signifies distance between most hydrophobic and hydrophilic point on the Van der Waals surface (vdW) surface.
5.	slogp	Log of the octanol/water partition coefficient (including implicit hydrogens). This property is an atomic contribution model that calculates logP from the given structure; i.e., the correct protonation state.

RESULTS AND DISCUSSION

Present investigation was aimed to evaluate the rapid release of IBP (acidic class) tablet formulations prepared using three different polymers. Subsequently, the evaluation parameters such as hardness, friability and *in vitro* DT were correlated with calculated set of polymeric physicochemical descriptors. This resulted into generation of statistical models with ability for early prediction of formulation composition.

Compatibility between Drug and Excipients

Identification of IBP and Standard Curve

IBP was identified by recording λ_{max} at 221 nm in hydrochloric acid buffer pH 1.2 *USP* as reported in previously results [9]. Calibration curve of IBP at λ_{max} (221 nm) indicated the correlation coefficient (r^2) as 0.9988; slope as 72.559 and intercept as +0.1003 in hydrochloric acid buffer (pH 1.2).

FTIR Spectroscopy

Additionally, pure drug (IBP) was identified by observing principal peaks in FTIR spectroscopy using KBr method (Figure 1). FTIR spectra indicated the principal peaks for pure IBP at 2961.52 (CH_3 asymmetric stretching vibrations); 2874.38 (CH_2 asymmetric stretching vibrations); 1716.34 (C=O stretching vibrations); 1512.88 (aromatic C=C stretching vibrations); 1421.28 (CH-CO deformation); 1325.82 (OH in plane deformation); 1231 (C-C stretching); 1072.23 (=C-H in plane deformation); 866 (C-H out of plane deformation); 785.85 (CH_2 rocking vibrations) which were in agreement with previously reported reference peaks. This confirmed the molecule as *α*-Methyl-4-(2-methylpropyl) benzeneacetic acid [12-14].

Additionally, all these principal peaks were found to be retained with very small or negligible shifting in all tablet formulations (F1 to F3) indicating compatibility between IBP and polymers in tablet formulation (Figure 1). Therefore without losing the potency, IBP can be effectively formulated into tablet formulations with use of selected polymers.

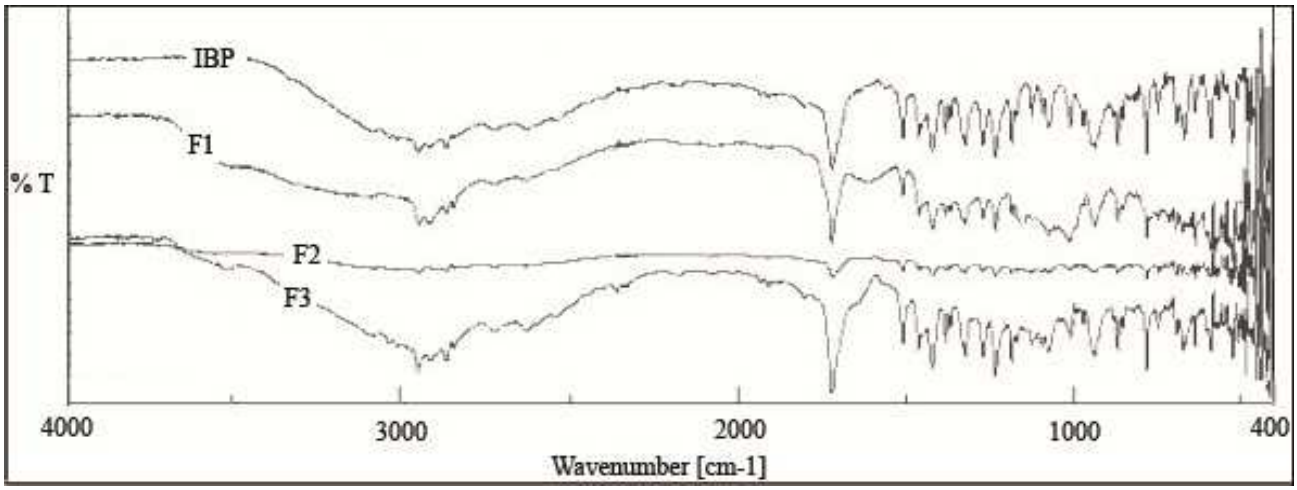

Figure 1: FTIR Spectrum of Pure IBP and Tablet Formulations (F1 to F3).

Characterization of Tablet Formulations

All tablets prepared for each batch (F1 to F3) were found to be with zero defects and smooth surface, flat in shape without change in odour, colour as well as no any signs of sticking and capping. Following post-compression parameters have been estimated for prepared IBP tablets from all batches.

Table 3: Evaluation parameters for IBP tablets*

Batch Code	F1	F2	F3
Uniformity of Weight (% deviation)	0.21 ± 0.33	0.52 ± 0.42	0.41 ± 0.53
Drug Content$^{\#}$ (%)	98.12 ± 1.97	101.32 ± 2.24	100.09 ± 1.53
Hardness$^{\#}$ (Kg/cm^2)	4.42 ± 0.06	4.36 ± 0.05	4.30 ± 0.05
Friability$^{\#}$ (%)	0.157 ± 0.035	0.277 ± 0.032	0.323 ± 0.032
Thickness$^{\#}$ (mm)	3.97 ± 0.029	3.99 ± 0.056	3.98 ± 0.044
Diameter$^{\#}$ (mm)	11.97 ± 0.028	12.02 ± 0.047	11.99 ± 0.018
Disintegration Time$^{\#}$ (sec)	57.33 ± 4.04	35.67 ± 5.03	20.00 ± 5.56

**All values are expressed as Average ± SD, where n = 3$^{\#}$.*

Uniformity of Weight

The lower percent deviation observed between 0.21 ± 0.33 and 0.52 ± 0.42 % (Table 3) indicated uniformity in weight of tables from all batches (F1 to F3) within range of acceptable official standards (± 5% deviation for 250 mg or more average weight) [6]. This was due to the good flow characteristics of granules, uniform die filling for constant weight that resulted into compression of tablets for constant hardness.

Drug Content

Uniformity in drug content has been observed for all tablet formulations (F1 to F3) between 98.12 ± 1.97 to 101.32 ± 2.24 % (Table 3) of IBP which was within the acceptable standards as ibuprofen tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of $C_{13}H_{18}O_2$ [15].

Hardness

All tablet formulations (F1 to F3) possesses good mechanical strength with sufficient hardness between 4.30 ± 0.05 and 4.42 ± 0.06 Kg/cm^2 (Table 3) to encounter the mechanical vibrations. Good hardness of tablet is indicative of increased densification and reduced porosity with net effect of higher time required for tablet disintegration. Observed hardness for all tablet formulations was in good agreement with results observed for tablet friability and DT.

Friability

Friability for all batches (F1 to F3) was observed within range of 0.157 ± 0.035 to 0.323 ± 0.032 % (Table 3) that complies with the prescribed pharmacopeial limits of not more than 1% [10]. Inverse relationship between friability and harness of tablet has been observed. Lower friability observed is suggestive of tablets with good handling property and resistance against the mechanical vibrations encountered during processes associated with machine, packaging and transport.

Tablet Dimensions

The results for thickness (3.97 ± 0.029 to 3.99 ± 0.056 mm) and diameter (11.97 ± 0.028 to 12.02 ± 0.047 mm) of tablets from all batches (F1 to F3) has been observed (Table 3) within the allowed limits (± 5%) of the tablet size indication uniformity in tablet dimensions.

In vitro DT

In vitro disintegration study was performed to ascertain the complete availability of drug from its dosage form for dissolution and hence absorption across the biological membrane. It has been observed that the faster rate of water penetration inside the tablet leads to reduction in time required for disintegration and dissolution. Therefore addition of disintegrant with high and quick water uptake capacity in tablet is preferable for faster disintegration of tablet. Additionally, particles of disintegrant found to develop the high disintegration force which is the main cause responsible for tablet breaking by swelling phenomenon. *In vitro* disintegration test for tablets from all formulations indicated the faster rate of disintegration (within 60 sec).

In present study, the slower rate of tablet disintegration has been observed for batch F1 (57.33 ± 4.04 sec) containing SSG superdisintegrant. This was due to the comparative lower water uptake capacity and hence wetting ability of SSG than CCS and CPVP. However, tablets from batch F2 (CCS) showed intermediate DT (35.67 ± 5.03 sec) indicating faster disintegration than SSG. This was attributed to the faster wetting and swelling as the mechanism for disintegration of tablet. Relatively faster rate of disintegration of tablets (20.00 ± 5.56 sec) from batch F3 (CPVP as superdisintegrant) has been observed. This was related to the highly crosslinked structure of CPVP that allows the

faster and higher water uptake and entrapment of water molecules with net result of immediate swelling. Additionally, the faster capillary action of CPVP together with marked hydration capacity and very minute tendency for gel formation could have contributed for faster disintegration. It has been reported that CPVP preferred wicking as the major mechanism for disintegration of tablet.

It has been reported that disintegration of tablets containing SSG and CCS individually resulted into formation of coarse and fine primary particles, respectively. Hence, such difference in size of particles formed after tablet disintegration could have an considerable effect over the disintegration and ultimately on dissolution profile.

Development of a Statistical Model

After drawing and energy minimizing the molecular models of selected polymers using Vlife MDS 4.2 commercial software, more than 100 physicochemical descriptors or properties of each polymer were calculated. After correlation analysis, different sets of 5 descriptors were prepared (independent variables) and subsequently processed by MLR analysis with various physical characteristics of tablet formulations such as hardness, friability and DT of IBP (response variable) to generate at least 4 models. From this a best statistical model with high correlation coefficient and least standard error (Table 4) with acceptable precision and good quantitative predictability for each property under investigation.

Table 4: MLR analysis data for developed statistical models*

Sr. No.	Name of Parameter	Regression Coefficients		
		Hardness	Friability	Disintegration Time
1.	r^2	+0.9597	+0.9480	+0.9989
2.	F - test	14.2898 (Analysis is significant)	10.9347 (Analysis is significant)	551.6615 (Analysis is significant)
3.	Standard error	±0.0223	±0.0293	±0.9035
4.	Intercept (Mean response)	+2.996	+12.913	+400.714
5.	H-Acceptor Count	-0.204	+1.671	+47.289
6.	H-Donor Count	+0.188	-1.524	-40.698
7.	SA Hydrophobic Area	+0.005	-0.041	-1.173
8.	XA Most Hydrophobic Hydrophilic Distance	+0.172	-1.787	-55.213
9.	slogp	-0.218	+1.699	+45.881

**where r^2 and q^2 are calculated and predicted correlation coefficients.*

A statistical model for individual physical property of tablet formulation was explained as below:

Hardness

$$Hardness = -0.204 \times H\_AcceptorCount + 0.188 \times H\_DonorCount + 0.005 \times SAHydrophobicArea + 0.172 \times XAMostHydrophobicHydrophilicDistance - 0.218 \times slogp + 2.996 \ (\pm 0.0223) \quad \ldots 2$$

A statistical model developed for hardness (equation 2) showed good correlation between all 5 polymeric properties and hardness of IBP tablets (r^2 = +0.9597) with mean response as +2.996 and lowest standard error (±0.0223) as given in Table 4. F-test (14.2898) indicated that analysis is significant i.e. all independent variable are having significant impact over hardness of IBP tablet. Correlation coefficient (r^2 = +0.9597) indicated that 95.97 % of the change in hardness of IBP tablet can be explained by the change in the 5 independent variables. Therefore, developed statistical model (equation 2) in present study is having good predictability for hardness of IBP tablets on basis of the polymeric properties. 'H-Acceptor Count' showed a significant negative impact on tablet hardness (regression coefficient = -0.204, Table 4). 'H-Acceptor Count' descriptor specifies the number of hydrogen bond acceptors groups in polymer structure. This indicates a decrease in tablet hardness with use of a polymer having high hydrogen bond accepting ability. Hence, 'H-Acceptor Count' of polymer must be highly concerned in selection of polymer for formulating a dosage form with suitable hardness. However, 'H-Donor Count' exhibited a highest positive impact on hardness (regression coefficient = +0.188, Table 4) indicating increase in tablet hardness with inclusion of a polymer having high hydrogen bond donating ability. 'H-Donor Count' descriptor represents the number of hydrogen bond donor atoms in structure. Therefore, any polymer with higher 'H-Donor Count' indicates stronger bonding through hydrogen bond formation with drug that result into improved hardness of tablet. The observed results (regression coefficients) were in good agreement with general inverse relationship that exist between 'H-Donor Count' (+0.188) and 'H-Acceptor Count' (-0.204). Additionally, 'SA Hydrophobic Area' showed a least positive effect on hardness of tablet (regression coefficient = +0.005) as given in Table 4. 'SA Hydrophobic Area' descriptor represents a vdW surface that denotes the hydrophobic surface area (by Audry method using Slogp). The positive coefficient of regression signifies the increased hardness of tablet in presence of polymer with higher hydrophobic area. Subsequent to 'H-Donor Count', 'XA Most Hydrophobic Hydrophilic Distance' indicated a good positive impact on hardness (regression coefficient = +0.172, Table 4) as indicative of

increased tablet hardness and strength with addition of polymer with high polarity. 'XA Most Hydrophobic Hydrophilic Distance' descriptor calculates the distance between most hydrophilic and hydrophobic point on the vdW surface that indicates the polarity on polymer surface. Increase in distance leads into reduction into net polarity on polymer surface with net result of increase in hardness as like 'SA Hydrophobic Area'. However, 'slogp' indicated the highest negative impact on tablet hardness (regression coefficient = -0.218) as given in Table 4 representing reduced hardness and strength of tablet with increase in log of partition coefficient. 'slogp' descriptor signifies log of the octanol/water partition coefficient (including implicit hydrogens). This property is an atomic contribution model that calculates logP from the given structure; i.e., the correct protonation state. Hence a decrease in hydrophobicity (partition coefficient) relates to the reduced hardness as observed with results for 'SA Hydrophobic Area' and 'XAMost Hydrophobic Hydrophilic Distance' descriptors.

Friability

$$Friability = +1.671 \times H\_AcceptorCount - 1.524 \times H\_DonorCount - 0.041 \times SAHydrophobicArea - 1.787 \times XAMostHydrophobicHydrophilicDistance + 1.699 \times slogp + 12.913 \ (\pm 0.0293) \quad \ldots 3$$

Developed statistical model for friability (equation 3) indicated good correlation with all 5 polymeric descriptors or properties (r^2 = +0.9480) with lowest standard error (±0.0293) and mean response as +12.913 (Table 4). F-test (10.9347) indicated significant analysis. From correlation coefficient 94.80% of the change in friability can be elucidated by the change in the 5 independent variables. Therefore based on estimated polymeric properties the developed mathematical model shows a good quantitative predictability for tablet friability. From Table 4 a significant positive impact of 'H-Acceptor Count' on tablet friability (regression coefficient = +1.671) has been observed. Therefore, friability of tablet was found to be increased with addition of polymer having higher 'H-Acceptor Count'. This could be related to the weak physical bonding between polymer and drug in presence of other ingredients that compete simultaneously with drug for polymer surface forming tablets with poor mechanical strength. Conversely, 'H-Donor Count' showed negative effect on friability (regression coefficient = -1.524, Table 4) specifying reduced friability of tablet with incorporation of a polymer having high hydrogen bond donor capacity. Polymer with higher 'H-Donor Count' indicates stronger bonding through hydrogen bond formation with drug that forms harder tablet with net result of reduce friability. The observed results (regression coefficients) were in good agreement with the general inverse relationship likely to have between 'H-Donor Count' (-1.524) and 'H-Acceptor Count' (+1.671). Additionally, 'SA Hydrophobic Area' showed a least negative impact on tablet friability (regression coefficient = -0.041, Table 4) which is also in good agreement with results observed for hardness. Negative regression coefficient indicates the reduced friability and improved hardness with increase in hydrophobic area. Highest negative impact (regression coefficient = -1.787) on friability of tablet has been observed with 'XA Most Hydrophobic Hydrophilic Distance' as shown in Table 4. This indicates a formation of less friable tablet with improved strength against mechanical shocks with reduction in polarity or with increase in distance between most hydrophilic and hydrophobic point on polymer. Conversely, 'slogp' showed highest positive impact on tablet friability (regression coefficient = +1.699, Table 4) representing increased friability and hence poor hardness and strength related to increase in log of partition coefficient (logP) or hydrophobicity. Observed results for 'slogp' were found to be in good agreement with hardness in terms of 'XA Most Hydrophobic Hydrophilic Distance' and 'SA Hydrophobic Area'.

DT

$$DT = +47.289 \times H\_AcceptorCount - 40.698 \times H\_DonorCount - 1.173 \times SAHydrophobicArea - 55.213 \times XAMostHydrophobicHydrophilicDistance + 45.881 \times slogp + 400.714 \ (\pm 0.9035) \quad \ldots 4$$

From a mathematical model developed for DT (equation 4), best correlation between 5 descriptors and DT (r^2 = +0.9989) has been observed. The model exhibited significant analysis (F-test = 551.6615) with mean response as +400.714 and minimum standard error (±0.9035, Table 4). Correlation coefficient indicates that the change in 5 independent variables can describe a change of 99.89% in DT of IBP tablets. Hence, on basis of calculated physicochemical properties the developed statistical model could be able to predict the DT for IBP tablet formulations. 'H-Acceptor Count' showed a highest significant positive impact on DT of tablet (regression coefficient = +47.289) as given in Table 4. Accordingly, slower disintegration of tablet has been observed with inclusion of polymer having high hydrogen accepting capability. This was attributed to the initial strong hydrogen bonding formed between drug and polymer where water molecules from immersion fluid compete simultaneously with drug for hydrogen bonding sites available with polymer. This resulted into increased wetting and hence DT of tablet. Conversely, an opposite and equal negative effect of 'H-Donor Count' on DT has been observed (regression coefficient = -40.698, Table 4) that indicates faster disintegration of tablet in presence of polymer with high 'H-Donor Count'. After contacting with disintegration fluid, polymer with high hydrogen bond donor capacity readily forms H-bonding with water molecules and simultaneous detaching the H-bonding formed with drug causing faster

disintegration of tablet. However, a comparatively negligible negative impact of 'SA Hydrophobic Area' on tablet DT (regression coefficient = -1.173, Table 4) has been observed. Negative sign for regression coefficient indicated a decrease in DT associated with increased hardness of tablet as hydrophobic area on polymer gets increased but the impact of this descriptor on DT is very small and hence can be neglected. Moreover, 'XA Most Hydrophobic Hydrophilic Distance' showed the highest negative impact (regression coefficient = -55.213, Table 4) on DT of IBP tablet. Hence, a very faster disintegration of tablet can be achieved with use of a polymer having high distance between most hydrophobic and hydrophilic point on polymer surface. This may lead to further separation of hydrophobic and hydrophilic points that may cause induction of localized polarity on surface of polymer with net result of increased wetting and reduced DT. Alternatively, 'slogp' showed significant positive effect on DT of tablet (regression coefficient = +45.881, Table 4) next to 'H-Acceptor Count' indicating increased time for disintegration with decrease in log of hydrophobicity or partition coefficient (logP).

Hence, 'H-Acceptor Count', 'H-Donor Count', 'XA Most Hydrophobic Hydrophilic Distance' and 'slogp' physicochemical properties of polymer must be greatly concerned in selection of a polymer or polymer system for formulating a dosage form with suitable characteristics. Conversely, the developed statistical models could be used in early prediction of formulation composition for desired hardness, friability and DT with acceptable precision.

CONCLUSION

Statistical models developed in present research could help to predict the hardness, friability and DT for dosage form which not yet formulated on basis of the physicochemical properties showing significant impact. Generated data can also be used to predict the formulation characteristics for other polymers showing identical physicochemical properties with polymers processed in current study. Therefore, formulation development based on statistical modelling could save time, material and formulation cost of pharmaceutical industry.

Acknowledgements
Authors are thankful to NuLife Pharmaceuticals (Pune, Maharashtra, India) for kind gift of ibuprofen.

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