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Experimental and chemoinformatics evaluation of some physicochemical properties of excipients influencing release kinetics of the acidic drug ibuprofen

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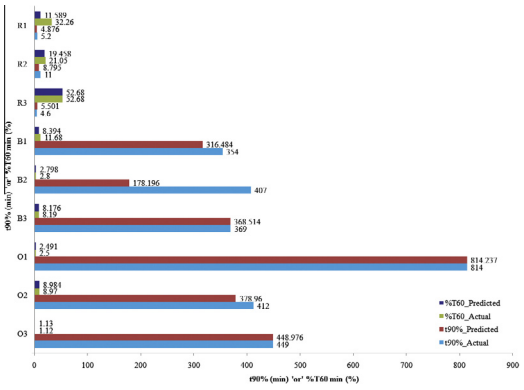
HIGHLIGHTS

- Molecular descriptors of polymeric structures were calculated.
- Formulation properties were correlated with calculated descriptors.
- This results into generation of QSPR models.
- Such models could be able predict the formulation properties and its composition.
- This could have pharmacoeconomic impact with saving of time and cost of formulation.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present study, ibuprofen, a nonsteroidal anti-inflammatory drug was used in the formulation of tablets using three polymers representing different categories (immediate, moderate and extended release). Prepared tablets were evaluated for different post-compression parameters including dissolution and transportability studies. *In vitro* dissolution studies indicated Korsmeyer–Peppas as a best fit model, however, the transport of the drug was found to be influenced by its rate of release. A total of 118 molecular descriptors representing physicochemical and topological properties of polymeric structure was calculated and correlated with formulation characteristics for model generation. Further, predictive quantitative-structure property relationship models were developed for correlating polymeric descriptors with formulation properties containing acidic drug (ibuprofen). Developed models exhibited good predictability for formulation characteristics as indicated by squared correlation coefficients (>0.9). Such models could have an ability to predict the formulation properties as well as composition for desired characteristics with saving of time, material and cost.

Abbreviations: CCS, croscarmellose sodium; CMCS, carboxymethyl cellulose sodium; CPVP, crospovidone; EC10, ethocel 10 cp FP standard premium; ERS100, eudragit RS100; FTIR, Fourier transform infrared spectroscopy; HAB, hydrochloric acid buffer; HPC, hydroxypropyl cellulose; IBU, ibuprofen; MDS, molecular design suite; ME15, methocel E15 LV premium; MLR, multiple linear regression; MPPB, monobasic potassium phosphate buffer; PEG 6000, polyethylene glycol 6000; QSPR, quantitative-structure property relationship; SD, standard deviation; SSG, sodium starch glycolate; USP, United States pharmacopoeia.

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1. Introduction

Excipients along with their conventional use must also control the drug dissolution, improve drug effectiveness and reduce dosing frequency with assured patient compliance. It has been reported that most of the excipients used under different categories are polymers (Moreton, 1995).

Recent pharmaceutical research is focused on developing a novel or modified drug delivery technology that assures complete delivery of the drug to the site of action. This can be achieved with the use of suitable polymer system in the formulation which decides the mechanism, rate and extent of drug release. For selection of proper polymer system one needs a comprehensive knowledge of physicochemical descriptors of a polymer. Such properties represent wettability, disintegration and dissolution of the drug and hence its bioavailability from a dosage forms (Grover et al., 2000a, 2000b). Polymer selection based on such properties often results in the formulation with desired characteristics as these properties are likely to have good correlation with the rate and extent of drug release. Hence, selection of the proper polymer composition is one of the critical steps involved in the formulation of a dosage form.

QSPR is based on the assumption that the information contained within the molecular structure can determine the related physical, chemical, and biological properties through calculation of one or more molecular descriptors (Grover et al., 2000a, 2000b). Predictive QSPR models for formulation design could be developed by accumulation and compilation of data generated from calculation of polymer properties and formulation characteristics. Such models could have an ability to predict the formulation composition with desired properties without formulating it. This could assist formulation design work with saving of time, material and cost of formulation (Gaikwad and Bhatia, 2013; Riera-Fernández et al., 2012).

Therefore, the present research was an attempt to get predictive models or a broader correlation between various physicochemical descriptors of diverse classes of polymers and their influence on the release and transportability properties of the formulation containing acidic drug (IBU). IBU is one of the original nonsteroidal anti-inflammatory drugs used in an effective management of mild or moderate pain, inflammation and stiffness. Tablet formulations were prepared using three different polymers, each of three different formulation categories (immediate, moderate and extended release) representing either cellulose semi-synthetic or synthetic class. The polymers used were sodium starch glycolate, croscarmellose sodium, crospovidone for immediate release; methocel E15, polyethylene glycol 6000, carboxymethyl cellulose sodium for moderate release and ethocel 10 cp, hydroxypropyl cellulose, eudragit RS100 for extended release of IBU. Total nine batches of tablets were prepared and tested for various post-compression parameters including drug release and transportability studies. In dissolution studies, the time required for 90% release of the initial amount of drug ($t_{90\%}$) and in transportability testing, percent of drug amount transported at 60 min ($\%T_{60min}$) was recorded. Further, estimated properties of IBU tablets were correlated with calculated polymeric descriptors for generation of QSPR models.

2. Materials and methods

2.1. Materials

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

2.2. Methods

2.2.1. Characterization of drug and excipients

2.2.1.1. Identification and calibration curve. Identification of IBU was done using UV–Visible spectrophotometer (Shimadzu Corporation, UV-1800, Japan) within scanning range of 200–400 nm. The calibration curve of IBU was done separately in 100 mM HAB pH 1.2 and 50 mM MPPB pH 6.8 at observed λ_{max}. Both buffer solutions (pH 1.2 and 6.8) were prepared as per procedure defined in USP (USPNF, 1995a).

2.2.1.2. FTIR analysis. The pure drug (IBU) and tablets from each batch were subject to FTIR analysis to find out any structural or chemical changes in IBU in tablet formulation by KBr method using Jasco FTIR-4100 recording FTIR Spectrometer. Samples were scanned between 400 and 4000 cm^{-1} and the resolution was kept at 1 cm^{-1}.

2.2.2. Preparation of compacts

Nine batches of IBU granules (R1 to O3) were prepared by wet granulation technique as per composition given in Table 1. All ingredients were initially sieved through mesh size 180 μm (ASTM #80) to get powder mass with uniform particle size. Further screened powder was mixed with distilled water (granulating liquid) to obtain a wet mass. This wet mass was further screened through mesh size 850 μm (ASTM #20) and dried at 60 °C for 1 h in a hot air oven (Bio Technics India, Mumbai, Maharashtra, India). Uniform size granules were obtained by screening dried granules through mesh size 600 μm (ASTM #30). The granules were further mixed with magnesium stearate and aerosil (fumed silica) as a lubricant and glidant.

Tablets were prepared by compressing dried granules (600 ± 5 mg) using a 8-punch rotary tablet press machine (CIP Machineries Pvt. Ltd., Ahmedabad, Gujrat, India) having a 12 mm round, flat-faced punch and die set for constant hardness of 4–5 kg cm^{-2}. Subsequently, for hardening and elastic recovery to occur tablets were allowed to relax for 24 h at ambient condition (Krycer et al., 1982). After relaxation period tablets were evaluated for several post-compression parameters such as uniformity of weight, drug content, hardness, friability, thickness, diameter and *in vitro* drug release kinetics and transportability studies.

2.2.3. Evaluation of compacts

2.2.3.1. Uniformity of weight. From each batch twenty tablets were randomly selected and weighed separately using an electronic balance (AUX220, Shimadzu Corporation, Japan). Then average weight was calculated and compared with individual tablet weight for determination of % deviation. The tablet passes the uniformity of weight test if not more than two of the individual tablet weights