Carbohydrate Polymers 151 (2016) 593–599

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Quantitative structure property relationship modeling of excipient properties for prediction of formulation characteristics

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ARTICLE INFO

Article history:
Received 12 April 2016
Received in revised form 21 May 2016
Accepted 31 May 2016
Available online 2 June 2016

Keywords:
Quantitative-structure property relationship
Excipient
Dissolution
Mathematical modelling
Drug release kinetic

ABSTRACT

Quantitative structure property relationship (QSPR) is used to relate the excipient descriptors with the formulation properties. A QSPR model is developed by regression analysis of selected descriptors contributing towards the targeted formulation properties. Developed QSPR model is validated by the true external method where it showed good accuracy and precision in predicting the formulation composition as experimental $t_{90\%}$ (61.35 min) is observed very close to predicted $t_{90\%}$ (67.37 min). Hence, QSPR approach saves resources by predicting drug release from an unformulated formulation; avoiding repetitive trials in the development of a new formulation and/or optimization of existing one.

1. Introduction

Formulation design involves processes to ascertain appropriate excipients which may be reasonably used with APIs in the proposed dosage form for regulation of processes to achieve desired formulation characteristics. Moreover, comprehensive study of compatibility and suitability of a set of excipients for achieving targeted tablet properties is also necessary (Chen, 2006). Excipients are known to facilitate administration and modulate release of the active component from the dosage form. This is usually achieved with selection based on their physicochemical properties that tend to decide the formulation characteristics. They also have ability to stabilize the drug against degradation from the physiological environment prior to its release from the formulation (Bruni, Amici, Berbenni, Marini, & Orlandi, 2002).

The present work was aimed to develop the mathematical relationship between the formulation property under investigation (time required for 90% release of the total amount of drug, $t_{90\%}$) and physicochemical descriptors of excipients used in formulation. These excipients include a variety of carbohydrate polymers such as cellulose derivatives (CCS, MCC, HPMC K100M and K4M), starch and its derivatives [SSG] for preparation of tablet formulations.

Cellulose and its derivatives are organic polysaccharides (polymeric carbohydrates) that contain a linear chain of thousands of $\beta(1 \rightarrow 4)$ linked D-glucose units. MCC (partially depolymerized cellulose), CCS (Cellulose, carboxymethyl ether, sodium salt, crosslinked) derived from crosslinking of carboxymethylcellulose sodium and HPMC K100M or K4M (Cellulose hydroxypropyl methyl ether) are cellulose carbohydrate polymers used herein to modulate the drug release from prepared tablet formulations.

Other polysaccharides used in present study include Starch 1500® (partially pregelatinized maize starch with 73% amylopectin and 27% amylose) and SSG (Sodium carboxymethyl ether of starch). Additionally, lactose (β-D-galactopyranosyl-$[1 \rightarrow 4]$-D-glucose) used as diluent, is a polymeric carbohydrate, a disaccharide sugar derived from galactose and glucose.

Total seventeen batches of compacts with different composition were prepared using MET as a model drug and were subsequently evaluated for several post-compression parameters. Further, predictive QSPR model was developed by accumulation, compilation and analysis of data generated from calculated polymer properties

Abbreviations: API, active pharmaceutical ingredient; CCS, croscarmellose sodium; ENM, enalapril maleate; HPMC, hydroxy propyl methyl cellulose; IPA, isopropyl alcohol; MCC, microcrystalline cellulose; MDS, molecular design suite; MET, metformin hydrochloride; MLR, multiple linear regression; PVP, polyvinyl pyrrolidone; QSPR, quantitative structure property relationship; SSG, sodium starch glycolate; USP, United States Pharmacopeia.

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http://dx.doi.org/10.1016/j.carbpol.2016.05.114
0144-8617/

and formulation parameters (Gaikwad & Bhatia, 2013; Gaikwad, Bhatia, & Singhvi, 2015; Katritzky, Maran, Lobanov, & Karelson, 2000). The developed model was validated using both internal and true external validation methods. Most of the previously reported work is based on analysis of the API properties with respect to the formulation properties. However, majority of formulations contains one or few APIs in comparison to a large number of excipients which are rationally more likely to influence the formulation properties.

1.1. Hypothesis

Therefore, the present research is an attempt to establish reasonable correlations between excipient properties and the formulation characteristics by using a QSPR approach. Developed model could be able to predict the formulation characteristics based on the physicochemical properties of excipients used in the drug delivery system.

2. Experimental

2.1. Materials

MET, Starch and Starch 1500® were kindly gifted by VerGo Pharma Research (Goa, India). Micro Labs Ltd. (Goa, India) supplied ENM as gift sample. HPMC K4M and HPMC K100M, MCC, Polyox, IPA and Methanol (Merck Limited, Mumbai, Maharashtra, India); PVP K30 and PVP K90, Carbopol, SSG, CCS and Aerosil (Fischer Scientific, Mumbai, Maharashtra, India) were purchased. Research Lab (Mumbai, Maharashtra, India) supplied Mannitol, Talc, Lactose, Magnesium Stearate and Zinc Stearate. 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. Drug identification and calibration curve. MET solution was prepared in methanol and double distilled water (1:1) solvent system after assessment of solubility of MET in different solvents. The prepared solution was scanned within the range of 200–400 nm for identification purpose using UV–vis spectrophotometer (Jasco V-630, Japan). The calibration curve of MET was plotted at observed λ_{max} to obtain slope, intercept and correlation coefficient values by using quantitative modes of the instrument.

2.2.2. Preparation of tablet formulations

A wet granulation method was used to prepare seventeen batches of MET granules (F1–F17) as per composition given in Table 1. All ingredients with uniform size were obtained by first powdering and subsequent sieving through ASTM #80 (mesh size 180 μm). Further, the powdered mass was evenly mixed and either of starch paste (20% w/v, F1), starch 1500® paste (20% w/v, F2), distilled water (F3 and F4), PVP K30 in IPA (F5 and F8–F11), PVP K30 (F6) and MCC (F7) and PVP K30 in distilled water (F12–F17) was added as binder to obtain a wet mass with desirable consistency. The wet mass was subsequently granulated by passing through ASTM #20 (mesh size 850 μm) and dried for 1 h at 40 °C in a hot air oven (Bio Technics India, Mumbai, Maharashtra, India). After confirming the low moisture content (3–5%), the uniformly sized granules were obtained by passing dried granules through ASTM #30 (mesh size 600 μm). However, for batches F8-F17, HPMC K100M and Carbopol were added to dried granules. Further, aerosil and magnesium stearate were added as a glidant and a lubricant, respectively and mixed for 5 min.

Tablets were prepared by compressing accurately weighed quantity of dried granules (Table 1) by using a 8-punch rotary tablet

Table 1
Formulation composition of MET compacts and validation batch (E).[a]

Name of Ingredient	Formulation Code																
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	E
MET	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	–
ENM	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5.27
Starch	31.25		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Starch 1500®	–	31.25	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
PVP K30	31.25	31.25	62.5	–	25	20	–	18	16	12	13	13	13	13	13	16	17	–
PVP K90	–	–	–	31.25	–	–	–	–	–	–	–	–	–	–	–	–	–	–
MCC	62.5	62.5	62.5	93.75	20	20	20	–	–	–	–	–	–	–	–	–	–	–
CCS	12.5	12.5	12.5	12.5	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SSG	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
Polyox	–	–	–	–	–	240	240	–	–	–	–	–	–	–	–	–	–	–
HPMC K4M	–	–	–	–	240	–	–	–	–	–	–	–	–	–	–	–	–	–
HPMC K100M	–	–	–	–	–	–	–	300	200	250	300	240	300	200	250	300	240	–
Carbopol	–	–	–	–	–	–	–	90	190	190	190	190	90	190	190	190	190	–
IPA	–	–	–	–	q.s.	–	–	45	45	50	55	–	–	–	–	–	–	–
Mannitol	–	–	–	–	–	–	6	–	–	–	–	–	–	–	–	–	–	–
Lactose	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	80.23
Distilled Water (mL)	–	–	–	–	–	–	–	–	–	–	–	35	35	30	30	30	30	–
Aerosil	–	–	–	–	–	5	5	–	–	–	–	–	–	–	–	–	–	1
Talc	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Magnesium Stearate	6.25	6.25	6.25	6.25	15	15	15	8	8	8	8	8	8	8	8	8	8	–
Zinc Stearate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1.5
Total weight of compact	643.5 ± 5	643.5 ± 5	643.5 ± 5	643.5 ± 5	800 ± 5	800 ± 5	786 ± 5	961 ± 5	959 ± 5	1010 ± 5	1066 ± 5	986 ± 5	946 ± 5	941 ± 5	991 ± 5	1044 ± 5	985 ± 5	110 ± 5

[a] All quantities of ingredients are expressed in mg.