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Preformulation studies and characterization of the physicochemical properties of amorphous polymers using artificial neural networks

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Abstract

The utility of artificial neural networks (ANNs) as a preformulation tool to determine the physicochemical properties of amorphous polymers such as the hydration characteristics, glass transition temperatures and rheological properties was investigated. The neural network simulator, CAD/Chem, based on the delta back-propagation paradigm was used for this study. The ANNs software was trained with sets of experimental data consisting of different polymer blends with known water-uptake profiles, glass transition temperatures and viscosity values. A set of similar data, not initially exposed to the ANNs was used to validate the ability of the ANNs to recognize patterns. The results of this investigation indicate that the ANNs accurately predicted the water-uptake, glass transition temperatures and viscosities of different amorphous polymers and their physical blends with a low % error (0–8%) of prediction. The ANNs also showed good correlation between the water-uptake and changes in the glass transition temperatures of the polymers. This study demonstrated the potential of the ANNs as a preformulation tool to evaluate the characteristics of amorphous polymers. This is particularly relevant when designing sustained release formulations that require the use of a fast hydrating polymer matrix.

Keywords: Preformulation studies; Amorphous polymer; Characterization; Artificial intelligence

1. Introduction

The majority of commercially available pharmaceutical sustained release matrix systems consist of swellable polymer such as cellulose ethers, polyvinylpyrrolidone (PVP), sodium alginate, etc. (Alderman, 1984; Kaul and Venkatalam, 1992; Dhopeshwarkar and Zatz, 1993; Ebube et al., 1997a). These amorphous polymers are capable of interacting with water at various stages of processing such as wet granulation or at high atmospheric moisture (Zografi and Oksanen, 1993; Ebube et al., 1996). The interaction between the amorphous polymers and water has been reported

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to result in marked changes in solid state properties of the polymers such as flow characteristics, dissolution rate, compactibility and glass transition temperature (Ahlneck and Zografi, 1990). A thorough knowledge of the underlying mechanism involved in water-polymer interaction will provide a better understanding of the physicochemical factors that influence drug release. This may require carefully designed preformulation studies, which are usually cumbersome, and often times very expensive.

The artificial neural networks (ANNs), which is composed of a series of non-linear operators, can identify and learn correlative patterns between input and output data pairs (Hussain et al., 1991; Achanta et al., 1995). ANNs are based on attempt to simulate the neurological abilities of the brain such as learning, generalizing, or abstracting from experience. These systems have the ability to discern relationships of patterns in response to exposure of facts (Bourquin et al., 1997). A major advantage of ANNs compared to statistical modeling is that they do not require rigidly structured experimental designs and can map functions using historical or incomplete data. Detailed description of the neural network architecture and computation of the neural output has been reported by (Erb, 1993; Bourquin et al., 1997; Ebube et al., 1997b).

Neural networks have been extensively applied, effectively and efficiently, to solve numerous problems in a variety of disciplines (Achanta et al., 1995). The utility of artificial neural networks in the pharmaceutical field has recently gained enormous interest in the pharmaceutical literature due to their ability to model processes that cannot be modeled by classical methods (Hussain et al., 1993, 1994; Murtoniemi et al., 1993; Turkoglu et al., 1995; Kurnik et al., 1999). A new area for the application of ANNs is in preformulation studies and material characterization, which are necessary to facilitate rational and optimal pharmaceutical product development.

Therefore, the objective of this investigation was to use the artificial neural networks to predict the physicochemical properties of amorphous polymers such as the hydration characteristics, glass transition temperatures and rheological properties. Thus, the overall goal of this study was to investigate the utility of the ANNs as a preformulation tool in pharmaceutical product development.

2. Materials and methods

2.1. Materials

The polymers used in this study were as follows: hydroxypropyl methylcellulose (HPMC: Methocel® K4M and E4M, DOW Chemical Co., Michigan, USA), hydroxypropyl cellulose (HPC: Klucel® LF, Aqualon, Deleware, USA), polyvinylpyrrolidone (PVP: K 29-32, International Specialty Products, New Jersey, USA), sodium alginate (Keltone® HVCR, Kelco Co., Chicago, IL), and carregeenan (Gelcarin®, FMC Corporation, PA, USA). All materials were used as received without further purification.

2.2. Methods

2.2.1. Polymer hydration studies

The gravimetric method reported by Gerogianis et al. (1993) was used to determine the % water-uptake by the amorphous polymers. A simplex centroid design was used to generate the composition of the various polymer matrices studied (Table 1a). Polymer samples consisting of either HPMC (K4M), polyvinylpyrrolidone (PVP), sodium alginate (Na ALG), carregeenan (CARGN) or their physical blends were filled into a size # 2 hard gelatin capsule, weighed and suspended into a beaker holding about 150 ml deionized water (pH 5.9). The weight of the swollen polymer samples was recorded at different time intervals up to 4 h. Water uptake by an empty size # 2 gelatin capsule was also determined and used as a control since hard gelatin capsule is capable of absorbing some water. The water sorption characteristics of the polymers or their various blends were expressed in terms of the % water uptake (WU_T) using Eq. (1)

$$WU_T = 100\left[\frac{W_{SC}}{W_{IC}} - 1\right] \quad (1)$$

where WU_T is the % water uptake of the polymer based on total weight (g) of the filled gelatin capsule, W_{SC} is the weight (g) of swollen form at time, t, and W_{IC} is the initial weight (g) of form at time, t_0. In order to account for the water uptake by the empty gelatin capsule, the % water uptake of the polymer (WU_{AW}) was calculated based on adjusted weight (g) using Eq. (2)

$$WU_{AW} = 100\left[\frac{W_{SC} - W_{GC}}{W_{IC} - W_{GC0}} - 1\right] \quad (2)$$

where W_{GC} is the weight (g) of empty gelatin capsule at time, t, and W_{GC0} represents weight (g) of empty gelatin capsule at time, t_0. All the water uptake experiments were carried out in triplicate and the results were expressed as the mean ± S.D.

2.2.2. Neural network analysis

A neural network simulator (CAD/Chem, version 5.0 Computer Associates, Cleveland, OH), based on a multilayer backpropagation paradigm was used for this study. The software was run on a PC with Pentium 120 processor and Microsoft Windows 95. The software requires an initial selection of the number of hidden layers, hidden layer nodes, and training iterations, followed by optimization of these ANN variables (Ebube et al., 1997b). ANNs learn using a training pattern file consisting of a set of input–output data pairs (Dowell et al., 1999). The ability of the trained network to generalize is tested using a validation pattern file, which consists of data not involved in

Table 1a
Composition of matrix polymer, training and validation data used for the ANNs analysis of the polymer hydration data

Experiment number	Matrix polymer composition[a]				Mean % water-uptake				
	K4M	PVP	Na ALG	CARGN	Hydration time (min) at				
					15	30	60	120	240
Training set									
1	1.00	0.00	0.00	0.00	61	90	192	283	388
2	0.00	1.00	0.00	0.00	116	196	272	309	370
3	0.00	0.00	1.00	0.00	49	87	195	480	695
4	0.00	0.00	0.00	1.00	95	115	159	219	335
5	0.50	0.50	0.00	0.00	79	98	136	196	302
6	0.50	0.00	0.50	0.00	64	123	171	368	751
7	0.50	0.00	0.00	0.50	96	136	174	235	349
8	0.00	0.50	0.50	0.00	62	100	191	442	718
9	0.00	0.50	0.00	0.50	85	132	188	277	418
10	0.00	0.00	0.50	0.50	93	121	188	306	680
11	0.33	0.33	0.33	0.00	96	137	179	235	349
12	0.33	0.33	0.00	0.33	71	97	139	198	511
13	0.33	0.00	0.33	0.33	78	104	146	235	476
14	0.00	0.33	0.33	0.33	95	119	201	447	688
15	0.25	0.25	0.25	0.25	73	100	143	227	449
Validation set									
1	0.05	0.20	0.45	0.30	87	108	196	373	733
2	0.60	0.00	0.00	0.40	88	118	159	219	355
3	0.25	0.00	0.00	0.75	85	126	174	239	374
4	0.25	0.00	0.75	0.00	56	98	195	435	711
5	0.00	0.25	0.75	0.00	60	105	192	455	688
6	0.25	0.75	0.00	0.00	93	135	193	278	351
7	0.00	0.00	0.75	0.25	66	104	195	423	731
8	0.00	0.75	0.25	0.00	91	156	224	358	426
9	0.75	0.00	0.00	0.25	74	101	169	219	361

[a] Represents fraction of each polymer in the matrix.

training of the network. Success of the ANNs was based on the prediction of the validation profile.

The training and validation patterns for the polymer hydration studies are presented in Table 1a. Inputs in the training pattern files consisted of the matrix polymer composition whereas outputs were the values of % water-uptake at different time intervals (0–240 min). The training pattern file consisted of 15 triplicate input–output associations and the validation pattern was made of a similar set of nine data. The network was trained with four hidden layer nodes and 241 iterations.

2.2.3. Glass transition temperature (T_g) studies

The effect of water vapor sorption on the viscoelastic properties of various amorphous hydrophilic polymers has been studied (Ebube, 1994). Water uptake by amorphous polymer is mainly determined by the total mass of the solid and it is independent of the specific surface area (Zografi, 1988). The dissolved water in the amorphous polymer acts as a plasticizer to greatly increase the free volume of the solid by reducing hydrogen bonding between adjoining molecules of the solid and consequently reduce the glass transition temperature of the solid. The glass transition temperature of the solid is progressively reduced as more water is dissolved into the solid. The change in the polymer from the glassy state (below T_g) to the rubbery state (above T_g) is accompanied by changes in the viscoelastic properties of the polymer. Changes in glass transition temperatures of Polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC, Methocel® E4M) and hydroxypropyl cellulose (HPC, Klucel LF) as a function of relative humidity and water vapor sorption were investigated (Ebube, 1994). Samples of each polymer were exposed to various relative humidities, and the glass transition temperature of the polymer was measured at equilibrium moisture content using a Perkin Elmer DSC II. Various saturated salt solutions contained in a series of Pyrex glass or Nalgene desiccators were used to provide the desired relative humidities (Oksanen and Zografi, 1990). All the glass transition temperature experiments were performed in triplicate and the results were expressed as the mean $\pm$ S.D.

A training pattern file consisting of a set of inputs (relative humidity, equilibrium water vapor content) and output (T_g) was used for the ANNs analysis (Tables 2–4). The network was trained with four out of five replicate data sets and the fifth data set was used for validation. ANN model was developed for predicting the T_g of various polymers exposed to different moisture levels and various relative humidities using three hidden layer nodes at different iterations. Although, the experimental data used for this study was recorded earlier by Ebube (1994) the utility of ANNs to predict the physicochemical properties (T_g, viscosity and hydration) of amorphous polymer has not been previously attempted.

2.2.4. Prediction of polymer viscosity

ANNs was used to correlate viscosity of polymer solution with composition of polymeric matrix and also with changes in temperatures. Data from a previous study involving sustained release polymeric matrices was used for this study (Ebube, 1994). Polymer solutions consisting of HPMC, HPC and PVP were prepared and the

Table 1b
Correlation matrix obtained from the polymer hydration data

Hydration time (min)	Correlation for % water uptake for			
	K4M	PVP	Na ALG	Carrageenan
15	−0.13	0.31	−0.03	0.43
30	−0.08	0.26	−0.04	0.27
60	−0.39	0.18	0.31	−0.15
120	−0.33	0.01	0.67	−0.24
240	−0.19	−0.09	0.78	−0.11

Table 2
Comparison of predicted and actual glass transition temperatures (T_g) of HPMC at different relative humidities and water contents

Relative humidity	Eq. water content (g/100 g polymer)	Glass trans. temp.			R^2	Error (%)
		Actual[a]		Pred.[b] (ANNs)		
		Mean	S.D.			
0.113	0.8901	495.9	3.76	496.2	91.9	0.06
0.324	1.9621	499.5	1.91	490.6	97.5	1.78
0.560	3.4687	476.1	5.23	481.5	93.9	1.13
0.679	5.4834	466.7	6.53	466.5	90.6	0.43
0.836	12.1438	445.7	1.01	463.6	97.9	4.02

[a] Experimental T_g values were previously determined (Ebube, 1994).
[b] Predicted T_g values were determined by ANNs.

Table 3
Comparison of predicted and actual glass transition temperatures (T_g) of HPC at different relative humidities and water contents

Relative humidity	Eq. water content (g/100 g polymer)	Glass trans. temp.			R^2	Error (%)
		Actual[a]		Pred.[b] (ANNs)		
		Mean	S.D.			
0.113	0.6707	517.3	0.00	517.3	99.7	0.06
0.324	1.5878	509.3	3.43	508.3	93.8	0.26
0.560	3.0814	488.5	5.74	495.2	86.2	1.37
0.679	4.4492	486.1	3.07	482.6	84.4	0.72
0.836	11.1348	453.3	2.51	482.7	98.9	6.49

[a] Experimental T_g values were previously determined (Ebube, 1994).
[b] Predicted T_g values were determined by ANNs.

Table 4
Comparison of predicted and actual glass transition temperatures (T_g) of PVP at different relative humidities and water contents

Relative humidity	Eq. water content (g/100 g polymer)	Glass trans. temp.			R^2	Error (%)
		Actual[a]		Pred.[b] (ANNs)		
		Mean	S.D.			
0.113	2.0784	482.5	5.77	464.9	99.1	3.65
0.324	8.0405	463.6	2.12	468.8	85.3	1.12
0.560	16.3652	453.6	2.86	453.1	90.6	0.11
0.679	21.7768	449.0	1.07	449.9	97.2	0.20
0.836	34.0355	447.9	1.56	447.9	99.8	0.00

[a] Experimental T_g values were previously determined (Ebube, 1994).
[b] Predicted T_g values were determined by ANNs.

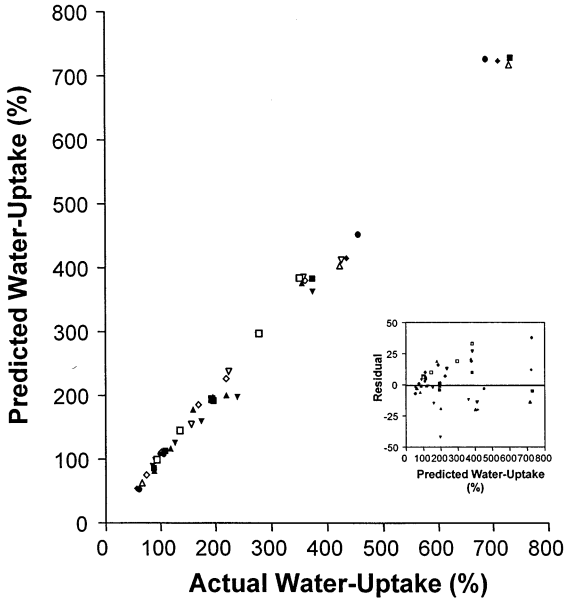

Fig. 1. Comparison of actual versus predicted water-uptake (%) for polymeric matrix contained in the validation set. Insert represents plot of residual versus predicted water-uptake (%).

viscosity of the polymer solutions was determined using a Brookfield viscometer (Model LVF). ANNs was trained with four out of five data sets and the fifth data set was used to validate the ability of the ANN model to generalize (Tables 5 and 6). For this study, the matrix polymer composition (HPMC + HPC) or temperature of polymer solution was used as the input, and the output was the viscosity of the polymer solution. All experiments were performed in triplicate and the results were expressed as the mean ± S.D.

3. Results and discussion

During the past two decades polymers which swell in aqueous medium have been extensively used for the preparation of oral sustained release dosage forms. For a matrix-type device (for example a tablet dosage form) in which the drug(s) is distributed as solid particles within the polymer, the polymer swells upon contact with an aqueous medium and forms a gel layer which then retards drug release. One of the important limitations of this type of device is dose dumping which is mainly facilitated by the inability of the matrix polymer(s) to hydrate rapidly to form a gel layer around the dosage form to regulate drug release. This may result in the release of a high dose of the drug(s) initially prior to the gel layer formation to retard drug release. This problem could be overcome by the use of a rapidly hydrating polymer that would form a gel layer of desirable consistency and hence drug release profile. The process of screening or selecting an ideal polymer or polymer matrix that will provide a target drug release profile is expensive and may involve extensive preformulation studies or hydration experiments. ANNs can identify and learn correlative patterns between input and output data pairs and thus show a good potential as a preformulation tool to characterize polymeric matrices.

Inputs from the training and validation pattern files derived from the polymer water uptake studies were applied to the trained networks, and the respective ANN outputs were compared to the actual observations. Fig. 1 shows a comparison of the actual versus predicted % water-uptake for different matrix polymer blends not initially exposed to the network. The insert is a plot of the residual as a function of predicted % water-uptake. The scatter plot clearly showed that the ANNs model accurately predicted the % water uptake of the different amorphous polymers studied with a low % error (0–8%) of prediction. The correlation matrix generated from the ANNs analysis is shown in Table 1b. This result indicates that the mechanism of hydration of the different polymers studied may vary for each polymer. Values of the correlation matrix may indicate that Methocel® K4M, unlike PVP, sodium alginate or carrageenan did not contribute considerably to the initial hydration (within 15 min) of the polymer matrix. The contribution of PVP to the hydration of a polymer matrix in which it is present was considerable initially (correlation value = 0.31 at 15 min), and its influence on polymer hydration decreased with time (correlation value = − 0.09 at 240 min). This result is consistent with the fact that capsules containing PVP alone absorbed wa-

ter rapidly, and did not form a gel as the PVP dissolved in water. Values of the correlation matrix as a function of time for sodium alginate increased with time and this result may indicate that sodium alginate influenced both the initial and latter matrix hydration. This is noteworthy as it demonstrated the potential of ANNs as an important preformulation tool in developing a sustained release formulation; especially when the choice of selecting a rapidly hydrating matrix is critical. However, it may be pertinent to mention that in general data obtained from the correlation matrix following ANNs analysis should be carefully evaluated based on available information derived from the experiment.

Tables 2–4 show a comparison of the predicted versus the actual glass transition temperatures for HPMC, HPC and PVP, respectively, as a function of equilibrium water content of the polymers at various relative humidities. The neural networks accurately predicted the glass transition temperatures of the amorphous polymers investigated with a low % error (0–6.5%). The R^2 values, which indicate the accountability of the ANNs model, were high and ranged from 84.4 to 99.7. The R^2 value was calculated using Eq. (3).

$$R^2 = \left(1 - \frac{\mathrm{SSE}}{\mathrm{SST}}\right)100 \quad (3)$$

where SSE is the error sum of squares and SST the total sum of squares. In cases of a poor model, where the error variance is greater than actual variance, the value of the R^2 may be less than 0 (CAD/Chem Reference Manual, Computer Associates, 1997).

Table 5
Comparison of actual and predicted viscosity of 2% polymer solution consisting of physical mixtures of HPMC and HPC

HPMC	HPC	Viscosity (cps)			R^2	Error (%)
		Actual[a]		Pred.[b] (ANNs)		
		Mean	S.D.			
1.00	1.00	561	0	1144	99.6	103.90
1.33	0.66	1240	26	1227	91.5	1.05
1.50	0.50	1820	6	1827	99.9	0.39
1.60	0.40	2310	6	2309	96.7	0.04
1.66	0.33	2620	6	2441	99.8	6.83

[a] Experimental viscosity values were previously determined (Ebube, 1994).
[b] Predicted viscosity values were determined by ANNs.

Table 6
Comparison of actual and predicted viscosity of 2% HPMC solutions at different temperatures

Temperature (°C)	Viscosity (cps)			R^2	Error (%)
	Actual[a]		Predicted[b]		
	Mean	S.D.			
25	4400	101	4032	99.6	8.36
31	3670	71	3638	85.7	0.87
37	2920	17	2942	93.6	0.75
43	2360	53	2381	90.7	0.89
50	1890	66	2173	99.7	14.90

[a] Experimental viscosity values were previously determined (Ebube, 1994).
[b] Predicted viscosity values were determined by ANNs.

Tables 5 and 6 show values of the predicted versus actual viscosity of 2% polymer solution consisting of either various blends of HPMC and HPC (Table 5) or 2% HPMC solution exposed to different temperatures (Table 6). Again, the ANNs model predicted the viscosity of the polymer solutions with a low % error and R^2 values ranging from 85.7–99.9. The % error obtained for predicting the viscosity of the polymer solution containing 1:1 HPMC:HPC (actual viscosity = 561 cps) was quite high (103.9%) because the actual viscosity value was considerably outside the range of data used for the training set. In a previous paper, a less accurate prediction of the response factor(s) by an ANNs model has been reported when input and response variables outside the range of the training set was used than for the data bounded by the training set (Ebube et al., 1997b). In establishing a design for ANNs analysis, sufficient data is needed to provide examples of all of the design space features to be mapped (Gill and Shut, 1992). This would enhance the accuracy of the ANNs model developed.

4. Conclusions

ANNs predicted the hydration characteristics (% water-uptake), glass transition temperatures and viscosity of amorphous polymers with good accuracy. Response variables outside the range of the training set reduced the accuracy of the ANNs model to estimate the response factors. The farther away the response factor is from the minimum or maximum range of the training set, the larger is the error. Overall, ANNs show a good promise as a useful preformulation tool in product development.

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