Genetic Programming Approach for the Modelling of Aspirin Extended Release Tablets

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Abstract— The objective of this work is to use genetic programming approach for the modelling of aspirin extended release tablets with Eudragit® RS PO as matrix substance. Genetic Programming involves several computer programs evolving towards the optimum solution and is an automated task. This property can be used to optimize and predict the dissolution of extended release Aspirin tablets. Eudragit® RS PO is the matrix substance in these tablets. The results show that there is no difference between experimental values and predicted values. This work illustrates potential of Genetic Programming to achieve a desired in vitro dissolution profile.

Key words: ASA Tablets, GP Model, ANNs

I. INTRODUCTION

Genetic Programming (GP) is a specialization of Genetic Algorithms. GP can solve problems automatically in which the user does need to know the structure or the form of the solution before solving it. A high level statement which tells what is required to be done is used to solve the problem. Every computer program generated has a fitness value which is a measure of how well a program can solve the problem [1, 5, 6, 7].

The Aspirin tablets are given in the oral dosage form and the dissolution testing was meant for studying these dosage forms. Nowadays, the drugs that are given in trans-dermal dosage forms are also used to perform dissolution testing as described in [11] The aim of the present study is to apply GP for the optimization of aspirin extended release tablets and show that the results are better than ANNs as given in [2]. These tablets have optimized release behaviour. The matrix substance for the tablets is Eudragit® RS PO. The amount of the matrix substance and the compression pressure which is expressed through the tablets hardness are the causal factors that are responsible for the release of aspirin. This release is observed over the period of eight hours with intervals as first hour, second hour, fourth hour and eighth hour [2, 8].

II. MATERIALS AND METHODS

The materials used in this work comprise of ECLIPSE IDE which is used for JAVA programming. The GP Model named as TinyGP is used to apply Genetic Programming. For optimization of Aspirin release, TinyGP program can be used with some modifications [1, 8, 9, 10].

A. ASA Tablets

The procedure used to prepare Aspirin extended release tablets is explained in [2, 3]. The tablets contain Eudragit® RS PO as matrix substance. The percentage of matrix substance i.e. Eudragit® RS PO and the compression pressure which is expressed through tablet hardness (N) are the factors responsible for cumulative aspirin release after an interval of eight hours. The release order n and the rate constant log k are used to characterize the release profiles. These values can be estimated using equation proposed by Peppas et al in [4].

B. GP Model

Poli in [1] proposed a model that can be used to apply GP methodology in a program named as TinyGP. With little modifications this program can be used to apply GP on in-vitro release data of ASA tablets so that new release data can be predicted when values of causal factors are provided. The input to this model is a data file which comprises of input values which are represented by the causal factors and the desired output which is in-vitro release values of ASA tablets.

The outputs are measured at the intervals of one hour, two hours, four hours and eight hours. Release order n and rate constant log k are also two another outputs for the GP Model. Six different data files are created according to above values each for every interval and remaining for values of n and log k. These data files are given as follows:

Formulation	Eudragit® RS PO (%)	Tablet Hardness	Release after one hour
1	5.41	35	22.01
2	6	57.5	15.17
3	2.58	80.5	16.19
4	5.41	80.5	10.9
5	4	90	12.59
6	2.58	35	22.8
7	4	57.5	20.77
8	4	57.5	18.72
9	2	57.5	14.37
10	4	25	23.26

Table 1: Input Data File 1

Formulation	Eudragit® RS PO (%)	Tablet hardness	Release after two hours
1	5.41	35	39.99
2	6	57.5	25.42
3	2.58	80.5	28.88
4	5.41	80.5	23.35
5	4	90	23.41
6	2.58	35	52.03
7	4	57.5	28.24
8	4	57.5	23.32
9	2	57.5	28.24
10	4	25	28.88

Table 2: Input Data File 2

Formulation	**Eudragit® RS PO (%)**	**Tablet Hardness**	**Release after four hours**
1	5.41	35	34.09
2	6	57.5	40.52
3	2.58	80.5	45.48
4	5.41	80.5	36.45
5	4	90	38.49
6	2.58	35	83.8
7	4	57.5	44.83
8	4	57.5	42.83
9	2	57.5	50.69
10	4	25	84.28

Table 3: Input Data File 3

Formulation	**Eudragit® RS PO (%)**	**Tablet Hardness**	**Release after eight hours**
1	5.41	35	99.5
2	6	57.5	63.76
3	2.58	80.5	58.28
4	5.41	80.5	56.28
5	4	90	55.74
6	2.58	35	94.51
7	4	57.5	68.16
8	4	57.5	69.23
9	2	57.5	77.4
10	4	25	99.06

Table 4: Input Data File 4

Formulation	Eudragit® RS PO (%)	Tablet Hardness	Release order n
1	5.41	35	0.738
2	6	57.5	0.676
3	2.58	80.5	0.607
4	5.41	80.5	0.754
5	4	90	0.702
6	2.58	35	0.651
7	4	57.5	0.588
8	4	57.5	0.579
9	2	57.5	0.793
10	4	25	0.701

Table 5: Input Data File 5

Formulation	Eudragit® RS PO (%)	Tablet Hardness	Rate constant log k
1	5.41	35	1.351
2	6	57.5	1.195
3	2.58	80.5	1.248
4	5.41	80.5	1.091
5	4	90	1.134
6	2.58	35	1.463
7	4	57.5	1.296
8	4	57.5	1.297
9	2	57.5	1.197
10	4	25	1.442

Table 6: Input Data File 6

C. GP Model Configuration

The first row of every data file contains values that decide the configuration of the GP Model. This first value indicates the number of inputs. Here the number of inputs is two which are the causal factors i.e. percentage of Eudragit® RS PO and tablet hardness N. The second value in first row is the number of random numbers to be generated. This number eventually represents the total number of iterations of GP Model we require. These iterations can be thought of as number of generations. Here this value is hundred. The third and fourth values in first row represent the lower limit and upper limit to generate random numbers. Here these values are taken as -1 and 1. The last value of the first row shows total number of entries in the input table. Here this value is ten. All the rows in input data file, except the first row, are regarded as fi fitness cases for the GP fitness cases for the GP Model. rows in input data file, except the first row, are regarded as fitness cases for the GP Model. The last value of the first row shows total number of entries in the input table. Here this value is ten. All the rows in input data file, except the first row, are regarded as fitness cases for the GP Model.

III. RESULTS AND DISCUSSION

The GP model was provided with input data file. At the end of execution, at last generation a function was obtained. This function was used in another program with test data. When this program is provided with test data the result obtained is the predicted value of Eudragit® RS PO or release order or rate constant depending on the input values given to program. The results obtained are tabulated as follows:

Formulation	**Experimental**	**Predicted**
1	22.01	22.011
2	15.17	15.17
3	16.19	16.186
4	10.9	10.896
5	12.59	12.5931
6	22.8	22.8
7	20.77	20.77
8	18.72	18.7198
9	14.37	14.37102
10	23.26	23.26121
Test 1	28.72	28.7078
Test 2	18.64	18.6037

Table 7: Prediction of %ASA Release after 1 Hour

The values in the first column are the results obtained after in-vitro ASA release in experiments. And the values in second column are the predictions obtained by the GP model.

Formulation	EXPERIMENTAL	PREDICTED
1	39.99	39.993
2	25.42	25.42
3	28.88	28.877
4	23.35	23.348
5	23.41	23.4101
6	52.03	52.03
7	28.24	28.236
8	23.32	23.32
9	28.24	28.2412
10	28.88	28.8803
Test 1	38.42	38.4199
Test 2	26.77	26.7699

Table 8: Prediction of %ASA Release after 2 Hours

Formulation	Experimental	Predicted
1	34.09	34.0913
2	40.52	40.518
3	45.48	45.4802
4	36.45	36.45
5	38.49	38.488
6	83.8	83.798
7	44.83	44.83
8	42.83	42.8302
9	50.69	50.69
10	84.28	84.276
Test 1	65.21	65.2932
Test 2	41.7	41.6999

Table 9: Prediction of %ASA Release after 4 Hours

Formulation	**Experimental**	**Predicted**
1	99.5	99.499
2	63.76	63.758
3	58.28	58.28
4	56.28	56.2698
5	55.74	55.7401
6	94.51	94.511
7	68.16	68.16
8	69.23	69.2316
9	77.4	77.401
10	99.06	99.06
Test 1	93.36	93.36227
Test 2	62.41	62.4016

Table 10: Prediction of %ASA Release after 8 Hours

Formulation	Experimental	Predicted
1	0.738	0.73811
2	0.676	0.67603
3	0.607	0.607
4	0.754	0.75411
5	0.702	0.70212
6	0.651	0.651
7	0.588	0.5882
8	0.579	0.579
9	0.793	0.79332
10	0.701	0.7011
Test 1	0.694	0.694
Test 2	0.589	0.59633

Table 11: Prediction of Release Order N

Formulation	Experimental	Predicted
1	1.351	1.35098
2	1.195	1.1946
3	1.248	1.24778
4	1.091	1.091
5	1.134	1.134
6	1.463	1.4627
7	1.296	1.29603
8	1.297	1.297
9	1.197	1.19668
10	1.442	1.442
Test 1	1.443	1.44296
Test 2	1.26	1.2587

Table 12: Prediction of Rate Constant Log K

Every row in above tables corresponds to a formulation based on respective values of causal factors i.e. percentage of Eudragit® RS PO and tablet hardness.

The comparison between the predictions obtained by GP Model and those obtained by artificial neural networks is given in following table 11. The test formulations are compared here only. The table shows that there is a huge difference between the experimental values and the predictions by ANNs. But the difference between the results obtained by GP Model and experimental results has very little difference or almost the same.

A. Comparison of Results

The comparison of results by GP Model with those by ANNs is tabulated as shown in following table 13. The test formulations are taken into consideration here.

Formulation		**Test1**	**Test2**
Eudragit ® RS PO (%)		6	2
Tablet Hardness		30	80
% ASA Released After 1 Hour	Experimental	28.72	18.64
	Prediction By GP	28.7078	18.6037
	Prediction By ANN	22.01	16.18
% ASA Released After 2 Hour	Experimental	38.42	26.77
	Prediction By GP	38.4199	26.7699
	Prediction By ANN	39.99	28.88
% ASA Released After 4 Hour	Experimental	65.21	41.7
	Prediction By GP	65.2932	41.6999
	Prediction By ANN	64.09	45.52
% ASA Released After 8 Hour	Experimental	93.36	62.41
	Prediction By GP	93.36227	62.4016
	Prediction By ANN	99.51	58.4
Value Of Release Order N	Experimental	0.694	0.589
	Prediction By GP	0.694	0.59633
	Prediction By ANN	0.738	0.609
Value Of Rate Constant Log K	Experimental	1.443	1.26
	Prediction By GP	1.44296	1.2587
	Prediction By ANN	1.351	1.248

Table 13: Comparison between the Predictions by GP Model and By ANN

The results show that the predictions made by using GP Model are better as compared to the results obtained by using Artificial Neural Networks. The ANNs perform very good with the training data but while performing with test formulations, the predictions made by ANNs are not doing so good. Unlike ANNs, the GP Model could predict accurately while using test data and even with the test data, the GP Model was good enough to accurately predict the values. Thus these results prove the applicability of GP Model for the modelling of Aspirin extended release

tablets. In future, Genetic Programming approach might perform the predictions without or very less amount of training data.

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