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Research paper

Modeling of a roller-compaction process using neural networks and genetic algorithms

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Abstract

In this study, roller-compaction of acetaminophene was studied to model the effect of binder type (hydroxypropyl methyl cellulose (HPMC), polyethylene glycol (PEG), Carbopol), binder concentration (5, 10 and 20%), number of roller-compaction passes (one or two), and extragranular microcrystalline cellulose addition on the properties of compressed tablets. Forty-two batches resulted from the experimental design. The artificial neural network methodology (ANN) along with genetic algorithms were used for data analysis and optimization. ANN and genetic models provided R^2 values between 0.3593 and 0.9991 for measured responses. When a set of validation experiments was analyzed, genetic algorithm predictions of tablet characteristics were much better than the ANN. Optimization based on genetic algorithm showed that using HPMC at 20%, with two roller-compaction passes would produce mechanically acceptable acetaminophene tablets. PEG and carbopol would also produce acceptable tablets perhaps more suitable for sustained release applications. Using PEG as a binder had the additional advantage of not requiring an external lubricant during tablet manufacturing.

Keywords: Roller-compaction; Acetaminophen; Artificial neural; Networks; Genetic algorithms; Mathematical modeling

1. Introduction

In pharmaceutical product development, experimental designs and mathematical modeling methods are well established [1–3]. As a newer approach, the artificial neural network systems (ANN) were used for data analysis by pharmaceutical researchers since the 1980s and it was shown that the ANN methodology performs well and it was a good candidate to replace multiple regression methods. Many comparative studies between regression and the ANN were also reported [4–6]. On the other hand, acetaminophene is a high dose drug with poor flow and compression characteristics [7–8]. Acetaminophen shows elastic deformation behavior upon compression and produces weak compacts [9]. Therefore, it is difficult to manufacture tablets without a prior agglomeration process. In this study, a roller-compaction process was applied to acetaminophen in the presence of three different binders at different binder concentrations and resulting tablets were evaluated for their characteristics. The purpose of this study was to model and evaluate an acetaminophen tablet manufacturing process based on roller-compaction by using neural network methodology along with the genetic algorithm to predict and optimize some tablet properties such as crushing strength, disintegration time and ejection force.

2. Materials and methods

2.1. Materials

Acetaminophene USP (Lot # 94-268-10-1, Rhone-Poulenc, Monmouth Junction, NJ), hydroxypropyl methyl cellulose (HPMC) (Methocel K4M, Dow Chemical, Midland, MI), polyethylene glycol (PEG) (Carbowax Compound 20M, Union Carbide, Danbury, CT), carbomer (Carbopol 974, BF Goodrich Speciality Chemicals, Cleveland, OH) and micro crystalline cellulose (MCC) (Avicel PH-302, FMC Corporation, Philadelphia, PA), were obtained as free samples for the study.

2.2. Equipment

Freund TF Mini roller-compactor (Freund Industrial Co. Ltd., Tokyo, Japan) was used as the main equipment. This system has a hopper mounted above the roller pair. A force

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feeding system consisting of a vertical feed screw located in the hopper conveys the material to the two counter-rotating compacting rolls. The compressed flakes or sheets were collected below the rolls. Throughout the process the roll-pressure was maintained at 70 kg/cm^2. Roll speed was kept between 6–9 rev./min, and feed speed was kept as 6–8 rev./min to maintain material flow. For processing roller compacted sheets and granules Turbula mixer (WAB Maschinenfabrik, Basel, Switzerland), Oscilating granulator (Erweka Model FGS, Erweka, Heusenstamm, Germany), Manesty D3B instrumented rotary tablet press that has the capability to monitor upper punch pressure and lower punch ejection force (Manesty Machines Ltd., Liverpool, UK) were used. For tablet testing Key hardness tester Model HT500II (Key International, Englishtown, NJ,), Erweka friabilator Model TAD, Erweka disintegration tester Model ZT were used.

2.3. Tablet formulation and manufacturing

Drug weight per tablet was kept constant as 325 mg throughout the study. Tablets contained acetaminophen, a binder (HPMC K4M, PEG 20M or Carbopol 974), talc, and MCC based on the experimental design. Process included a 10-min mixing of the drug with a binder and 3% talc in a Turbula mixer then the powder was passed through roller-compactor once or twice based on the experimental design. The next step was passing the dry-granulated sheet through an oscillating granulator prior to compression, for some batches 5% extragranular MCC was added and mixed for 5 min just before tableting stage. Tablets were compressed using a Manesty D3B instrumented rotary tablet press with 9 mm concave punches at 3000 lbs force and no lubricant was used during tablet compression. The lower punch ejection force was monitored during tableting. Disintegration test was carried out in water, for tablet crushing strength 20 tablets were tested for each batch.

2.4. Experimental design

In this study, a four level hierarchical design consisting of 42 experiments was used to evaluate the effect of three formulation and one process variable on roller-compacted acetaminophene tablets. Binder types were: HPMC, PEG, and Carbopol. Binder concentrations were studied between 5 and 20%. The number of compaction passes was the only process parameter that was studied as one or two passes. Finally, a 5% extragranular MCC addition was included in the design. Table 1 summarizes the experimental design including the 12 test experiments for model validation.

Table 1
Experimental design (non-randomized list of experiments) for roller-compaction of acetaminophen[a]

Experiment number	Binder type	Binder concentration (%)	Compaction passes	MCC addition[b]
1	HPMC	5	1	0
2	**HPMC**	**10**	**1**	**1**
3	HPMC	20	1	1
4	HPMC	5	2	0
5	HPMC	10	2	0
6	HPMC	20	2	0
7	HPMC	5	1	1
8	HPMC	10	1	0
9	**HPMC**	**20**	**1**	**0**
10	HPMC	5	2	1
11	HPMC	10	2	1
12	HPMC	20	2	1
13	**HPMC**	**20**	**2**	**1**
14	HPMC	20	2	1
15	PEG	5	1	0
16	**PEG**	**10**	**1**	**1**
17	PEG	20	1	1
18	**PEG**	**5**	**2**	**0**
19	PEG	10	2	0
20	PEG	20	2	0
21	PEG	5	1	1
22	PEG	10	1	0
23	**PEG**	**20**	**1**	**0**
24	PEG	5	2	1
25	PEG	10	2	1
26	PEG	20	2	1
27	**PEG**	**20**	**2**	**1**
28	PEG	20	2	1
29	Carbopol	5	1	0
30	**Carbopol**	**10**	**1**	**1**
31	Carbopol	20	1	1
32	**Carbopol**	**5**	**2**	**0**
33	Carbopol	10	2	0
34	Carbopol	20	2	0
35	Carbopol	5	1	1
36	Carbopol	10	1	0
37	**Carbopol**	**20**	**1**	**0**
38	Carbopol	5	2	1
39	Carbopol	10	2	1
40	Carbopol	0	2	1
41	**Carbopol**	**20**	**2**	**1**
42	Carbopol	20	2	1

[a] Bold characters are selected 12 experiments for testing constructed models.
[b] 5% Avicel addition.

2.5. Data analysis and model forming

2.5.1. Neural networks and genetic algorithm

An Artificial Neural Network (ANN) is a flexible data processing system and its architecture is similar to the biological neural networks. The primary part of ANN is a processing element that is called 'neuron'. The neurons are non-linear structures that sum the strengths of all its input signals and passes the sum through an 'activation function'. During the 'Learning Process' of ANN, which is a weight adjustment process, the most popular algorithm is the 'Delta Backpropagation Network'. A genetic algorithm solves optimization problems by creating a group of possible solutions (population) to the problem. The individuals in this population will carry (chromosomes) values of variables of a problem. The genetic algorithm actually solves optimiza-

Table 2
Lists of measured responses[a]

	EJECT[b] (lbs force)	CRUSH[c] (kp)	FRIAB[d] (%)	DISIN[e] (min)
1	30	1.41	100	3.6
2	**45**	**2.56**	**11.03**	**1.5**
3	85	8.26	0.21	6.4
4	**40**	**2.47**	**100**	**14**
5	50	2.88	0.63	3.4
6	80	8.29	0.21	11
7	40	1.50	79.89	2
8	35	2.10	41.15	1.3
9	**75**	**6.77**	**20.10**	**7**
10	50	2.82	59.90	3.7
11	70	4.59	10.06	2
12	110	9.37	0.09	5.5
13	**100**	**10.72**	**021**	**5.7**
14	105	10.12	0.16	7.1
15	15	1.49	100	49
16	**10**	**2.94**	**0.72**	**7.3**
17	10	6.16	0.21	57
18	**12**	**2.42**	**40.21**	**44**
19	12	3.64	0.45	51.3
20	12	7.14	0.23	70
21	15	1.88	90.20	8.5
22	10	2.88	0.77	53
23	**18**	**4.96**	**0.41**	**76**
24	15	2.62	30.45	8
25	10	5.07	0.24	35
26	15	9.61	0.12	75
27	**15**	**8.66**	**0.16**	**72**
28	15	8.77	0.14	63
29	25	2.93	100	98
30	**40**	**2.91**	**100**	**120**
31	75	5.46	10.48	240
32	**25**	**3.24**	**100**	**114**
33	35	3.76	100	120
34	60	4.14	40.42	240
35	40	2.12	100	97
36	30	2.33	100	120
37	**70**	**4.26**	**0.35**	**120**
38	45	2.94	100	120
39	55	3.77	90	110
40	85	4.85	0.29	240
41	**85**	**5.34**	**0.28**	**240**
42	85	4.78	0.45	240

[a] Bold characters are selected 12 experiments for testing constructed models.
[b] EJECT, Lower punch tablet ejection force.
[c] CRUSH, Tablet crushing strength.
[d] FRIAB, Tablet percent friability.
[e] DISIN, Tablet disintegration time.

tion problems by allowing the less fit individuals in the population to die and selectively breeding the most fit individuals (the ones that solve the problem best). The genetic algorithm similarly occasionally causes mutations in its populations by randomly changing the value of a variable. After hundreds of 'generations', a population eventually emerges wherein the individuals will solve the problem that will be an optimum solution. Further theoretical details of ANN and genetic algorithms can be found in the literature [4,10].

The data were analyzed using a commercial software package for neural networks and genetic algorithms (NeuroShell Easy Predictor, Ward Systems Group, Frederick, MD 21703, USA, 1997). Out of 42 experiments, 30 were used to train the network and 12 were used used to test the prediction capacity of neural network and genetic algorithm. Table 2 gives the measured responses for experiments. First using the data from 30 experiments models were formed. Those models were used to predict the outputs of those 12 experiments by the ANN and genetic algorithms.

3. Results and discussion

3.1. Results of ANN and genetic modeling

In Table 1, experimental design is shown. As a first step, 30 data points that is called 'training set' were selected to form a mathematical model. A set of 12 experiments were saved, (Table 1), as the 'test set'. A special care was given to select an evenly distributed set of experiments for the test data. To establish a mathematical connection between the independent variables that were binder type, binder concentration, compaction passes, and MCC addition and response variables that were tablet ejection force, crushing strength, disintegration time and friability, the artificial neural network methodology including the genetic algorithm was used in a similar manner that was previously reported in the literature [10].

Table 3 summarizes the models, the coefficients of determination (R^2), and the average error after the training session with 30 experimental data points. This table simply shows the ability of data analysis system to learn and generalize. Based on Table 3, CRUSH, DISIN and FRIAB were modeled successfully by both ANN and genetic approaches. Only EJECT could not be modeled by the ANN satisfactorily ($R^2 = 0.3593$) which meant the ANN could not detect low friction in the tablet press when PEG 20000 was used as a binder between 5 and 20%. However, using a genetic algorithm a R^2 value of 0.8859 for the ejection force could be achieved. Therefore, it seemed that reliable models could be formed using 30 training experiments.

The prediction power of those models remained to be tested. As the next step, the 12-experiment data set indicated in Table 1 was analyzed using constructed models and Table 4 summarized the results. On the contrary of high R^2 values of ANN models, their predictions of tablet characteristics were poor with the exception of tablet crushing strength ($R^2 = 0.9064$). The CRUSH predictions were comparable between ANN and genetic algorithms. For ejection force (EJECT), ANN system had an average error of 21 units, whereas, the genetic algorithm had an average error of 4.54 units with a high R^2 value (0.9633). Although trained model had a high R^2 value for tablet friability (FRIAB), the predictions of the ANN were very poor ($R^2 = 0.04320$).

Table 3
Results of models constructed using ANN and genetic algorithm using 30 experimental data points

	[ANN]			[Genetic]		
	R^2	Hidden neurons	Average error	R^2	Generations trained	Average error
EJECT	0.3593	16	20.05	0.8859	227	7.68
CRUSH	0.9968	24	0.071	0.8614	132	0.80
FRIAB	0.9748	24	4.62	0.8636	151	9.84
DISIN	0.9991	24	1.59	0.9900	286	5.57

Table 4
Predictions of tablet characteristics using ANN and genetic models based on 12 test experiments

	[ANN]			[Genetic]		
	R^2	Hidden neurons	Average error	R^2	Generations trained	Average error
EJECT	0.1862	16	20.72	0.9633	227	4.54
CRUSH	0.9064	24	0.070	0.9118	132	0.61
FRIAB	0.0432	24	471.0	0.8613	151	9.46
DISIN	0.0760	24	449.41	0.7271	286	15.88

Again genetic algorithm was reasonably successful in predicting tablet friability with a 9.46% average error. Tablet disintegration time (DISIN) was found to be a more difficult parameter to predict. For instance, the ANN produced a huge average error of 449.41 min, whereas the genetic algorithm predicted the DISIN within the range of 15.88 min of average error for 12 experiments. Overall, during model forming stage both ANN and genetic models were acceptable and powerful. However, during model evaluation the genetic algorithm was found to be more successful than plain neural network algorithm. Figs. 1–4 show the actual experimental responses for tablet ejection force, crushing strength, percentage friability and disintegration time values along with the predicted responses by the models of 12 test experiments. It was clear from the figures that genetic algorithm predictions were much closer to the actual ones.

3.2. Tablet characteristics based on the best models

Using the genetic algorithm, obtained tablet characteristics could be summarized below: For ejection force, binder type was found to be the most influential factor (15.40%), second important factor was the binder concentration, contribution to response was 10%, addition of extragranular (MCC) had a relative contribution about 8%, and the number of passes from roller compactor had the smallest effect (3.7%) on measured lower punch ejection force. Overall, PEG as a binder resulted in the lowest ejection forces (10–18 lbs force) and the values were not affected

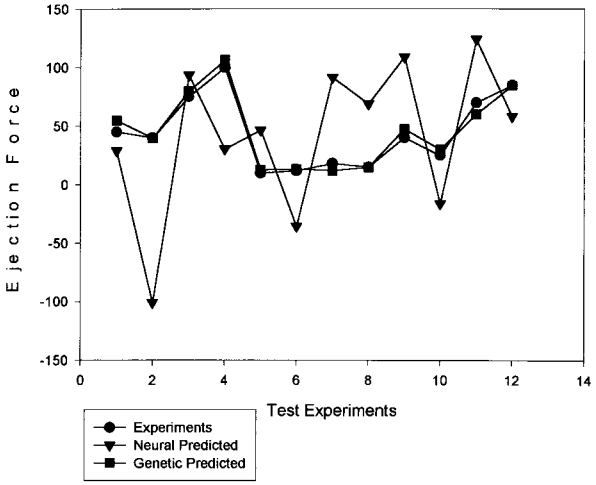

Fig. 1. Comparison of tablet ejection force values for 12 test experiments among observed, neural predicted and genetic predicted.

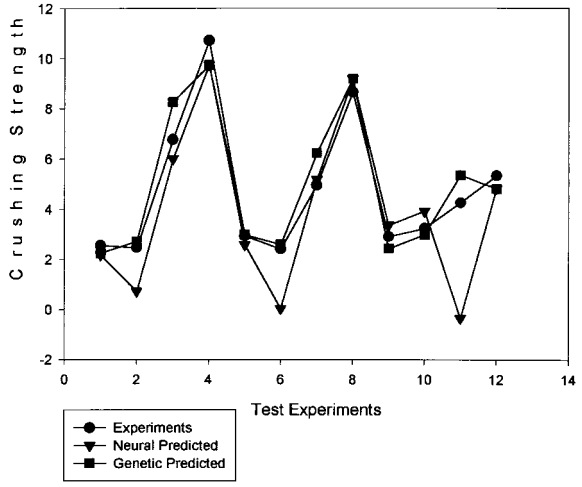

Fig. 2. Comparison of crushing strength values for 12 test experiments among observed, neural predicted and genetic predicted.

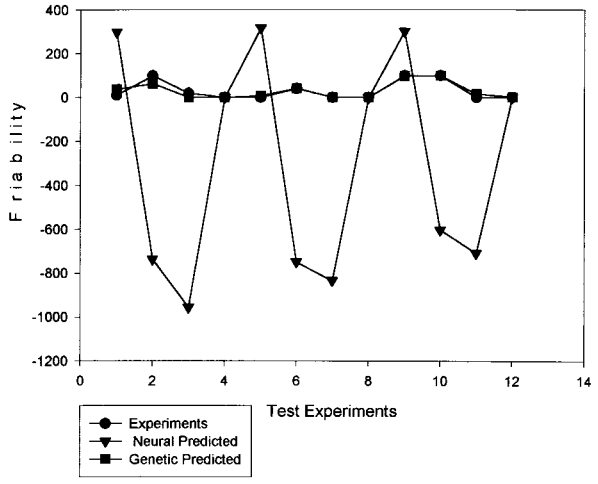

Fig. 3. Comparison of tablet friability values for 12 test experiments among observed, neural predicted and genetic predicted.

by the other factors significantly. When HPMC and Carbopol used in formulations, the ejection forces varied between 25–105 lbs force depending on other factor settings.

Binder concentration was the most significant factor on tablet crushing strength based on inputs' relative importance that resulted from genetic algorithm. It explained 27% of the response just by itself, binder type was the second influential factor (16.5%) of the response. Number of roller-compactor passes and MCC addition both had an effect in the range of 10%. The strongest acetaminophen tablets were obtained using a binder concentration of 20% with HPMC or PEG as dry binder, two roller compactor passes, and using 5% extragranular MCC. Under those circumstances a set of tablet crushing strength values of 8.5–11 kp could be obtained from this process.

Tablet friability was primarily affected by the binder type (relative influence 34%), binder concentration was the second important effect. Friability values less than 1% could be obtained by any of the binders at 20% binder concentration and two roller compaction passes. Twenty batches out of 42 resulted in tablets that show less than 1% friability in this study with acetaminophen.

No disintegrant was used in the formulation. In addition, Carbopol is such a material that it forms gel like structures rather than a disintegrating matrix. Hence, none of the batches made with Carbopol disintegrated within pharmacopeal time frames. When PEG concentration was 5%, tablets dissolved between 5 and 8 min, but any concentration above 5% resulted in tablets that dissolved slowly between 33 and 75 min. However, depending on the factor settings those batches containing HPMC provided disinte-

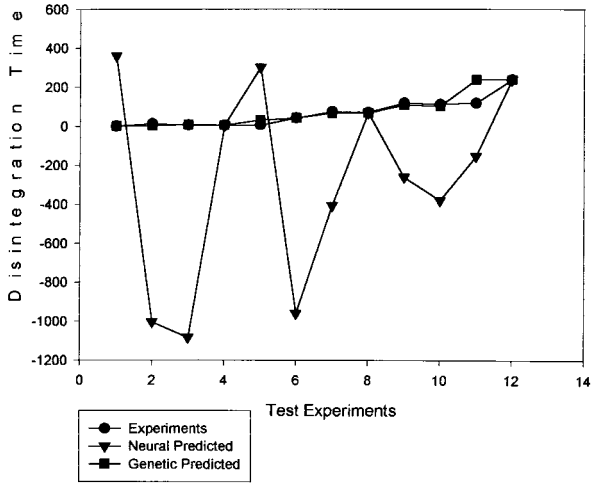

Fig. 4. Comparison of tablet disintegration time values for 12 test experiments among observed, neural predicted and genetic predicted.

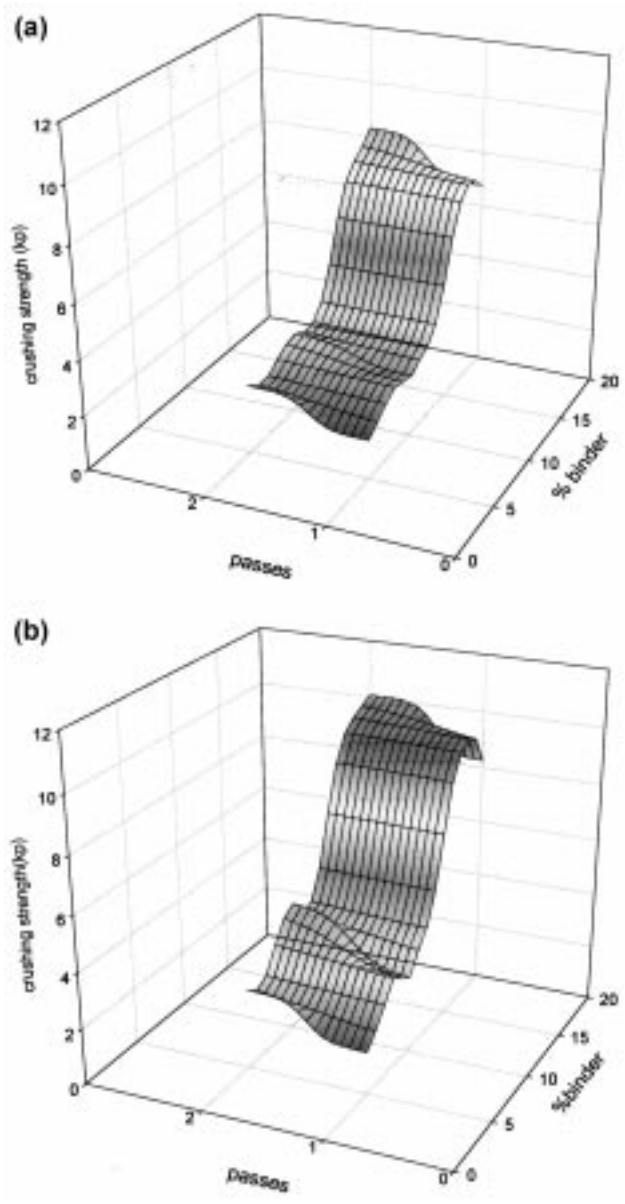

Fig. 5. (a) 3-D plot of tablet crushing strength predicted by the model for batches without extragranular MCC. Binder type, HPMC. (b) 3-D plot of tablet crushing strength predicted by the model for batches with extragranular MCC. Binder type, HPMC.

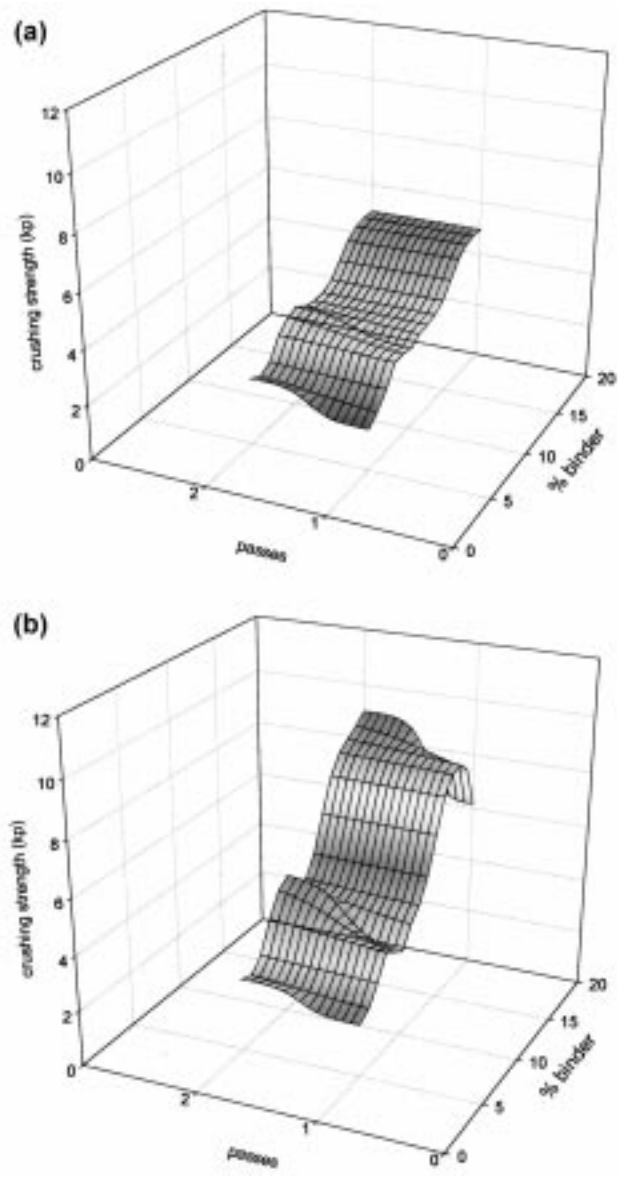

Fig. 6. (a) 3-D plot of tablet crushing strength predicted by the model for batches without extragranular MCC. Binder type, PEG. (b) 3-D plot of tablet crushing strength predicted by the model for batches with extragranular MCC. Binder type, PEG.

gration times between 1 and 14 min. Binder concentration was found to be the primary factor for disintegration time (14%), binder type had a relative influence as 11.45%, and MCC addition and number of passes were 5.49 and 4.55%, respectively.

For the case of acetaminophen the most important tablet characteristic was the tablet crushing strength. Because a mechanically durable tablet will also provide an acceptable percent friability value. Therefore, Figs. 5–7 shows the 3-D plots of number of roller-compactor passes vs. % binder with and without extragranular MCC addition. In those graphs, between one and two passes were artificially interpolated, hence only the lines of one or two passes should be considered and evaluated. Based on these 3-D graphs one can observe the effect of formulation and process variables on acetaminophene tablet crushing strength for three different binder types. Fig. 5 shows the case of HPMC as a binder: HPMC was the most promising binder type in terms of mechanically acceptable tablets. Two passes through roller compactor increased the compactability of the granules when compared with one pass and addition of MCC magnified the effect (Fig. 5b). Model indicates that starting from 12% HPMC tablets gain mechanical strength with a steep rise and reach a tablet hardness value of 10 kp at the two-pass portion of the graph.

As it can be shown in Fig. 6a,b, MCC addition to PEG resulted in a significant increase in tablet crushing strength.

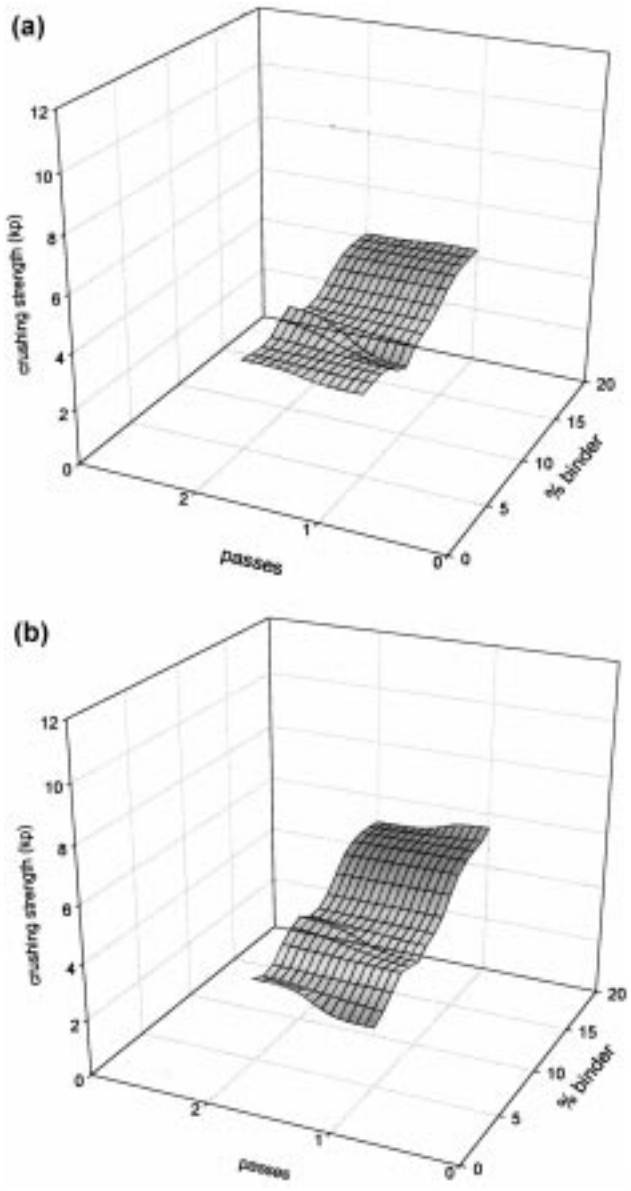

Fig. 7. (a) 3-D plot of tablet crushing strength predicted by the model for batches without extragranular MCC. Binder type, Carbopol. (b) 3-D plot of tablet crushing strength predicted by the model for batches with extragranular MCC. Binder type, Carbopol.

Table 5
Optimization of acetaminophen tablets based on genetic algorithm[a]

Process/formulation parameters

Batch	Binder type	Binder (%)	MCC (%)	Compaction pass
A	HPMC	20	0	2
B	HPMC	20	5	2
C	PEG	20	5	2
D	Carbopol	20	5	1

Obtained tablet characteristics

Batch	EJECT (lbs)	CRUSH (kp)	FRIAB (%)	DISIN (min)
A	85	8.60	0.58	10
B	105	9.98	0.16	6
C	15	8.90	0.15	70
D	85	5.05	1.00	240

[a] Constraints: CRUSH, $\geq$5.0; FRIAB, $\leq$1.0.

Passing two times from the roller compaction also improved the mechanical properties and at two pass and 20% PEG level a crushing strength value of 9 kp was obtained.

Effect of MCC on Carbopol was similar (Fig. 7a,b) to the effect on HPMC and PEG however, the magnitude was different. The highest hardness value of 5 kp could be obtained at about 20% binder level. The effect of one or two passes was less significant for Carbopol.

3.3. Optimization

Based on the genetic model, an optimization attempt was made and an optimum immediate release acetaminophen tablet formulation could be obtained using either HPMC K4M or PEG 20M as a binder type. A binder concentration more than 15% and two passes through roller-compactor are required. Furthermore, a 5% MCC addition would be required in the case of PEG20M. However, with HPMC K4M without extragranular MCC an optimum tablet could be obtained. Using Carbopol as a binder, a slow release acetaminophen tablet could be obtained with acceptable mechanical properties. For PEG20M, when the binder concentration exceeds 5% disintegration time becomes about 70 min. Using PEG, even as low as 5%, all the tablets were ejected from the tablet press less than 20 lbs force that meant tablet manufacturing with PEG 20M would not require external lubricant. Table 5 summarizes the constraints, target values and obtained tablet properties for the optimized batches.

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