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Research paper

# Tableting and stability evaluation of enteric-coated omeprazole pellets

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**Abstract**

In this study, fluidized-bed manufactured enteric-coated omeprazole pellets were compressed into tablets. The stability of the pellets and those of compressed tablets were evaluated for remaining omeprazole and for degradation products under an accelerated stability protocol. The data were analyzed using the artificial neural network (ANN) and analysis of variance (ANOVA). It was found that enteric-coated omeprazole pellets could be compressed into quickly disintegrating tablets using microcrystalline cellulose granules as the pressure absorbing matrix. The ANN, using the multilayer perceptron model, predicted that there was a positive correlation between tablet crushing strength and microcrystalline cellulose concentration. Microcrystalline cellulose matrix showed a strong plastic deformation and all the pellets inside the tablet maintained their integrity with no significant change in their surface properties. Omeprazole degradation in acid medium was mainly dependent on microcrystalline cellulose concentration. A 90-day accelerated stability test in brown glass bottles with a desiccant showed that all prototype formulations would result in an acceptable stability profile for both remaining omeprazole, and also for the increase of impurity concentrations.


*Keywords:* Pellets; Artificial neural networks; Pellet compression; Omeprazole; Accelerated stability

## 1. Introduction

Tableting of multiparticulate systems such as pellets and microspheres is an attractive approach to prepare a single unit dosage form that will readily disintegrate into its essential components when exposed to gastro-intestinal fluid. That type of dosage form will maintain the advantages of pellets despite being a tablet. There are two points of interest when compressing a coated particle. The first one is the effect of excipients, and the other is the composition and the amount of coating on the particle. In this study, we only investigated the effect of excipients on coated particles. The polymer type and the polymer/plasticizer ratio were kept constant for the optimized enteric-coated product. Maganti and Çelik reported that increasing the amount of polymer on the coated particles reduced their yield strengths and resulted in compacts with lower tensile strength and higher elastic recovery, pellets coated with increasing amounts of coating exhibited relatively more punch velocity dependence [1]. Schmidt et al. found that the most important factors were the coating polymer and the amount of coating when enteric-coating integrity was tested for bisacody pellets in acid medium after compression [2]. Another report by Schmidt et al. focused on the effect of excipients on enteric-coated pellets and for approximately 1 mm pellets, the larger size Avicel granules caused more deformation of pellets but less damage to the coating in comparison to Avicel PH 101 powder and it was also concluded that damage to the coating mainly occurred on the tablet surface during compression [3]. Beckert and Lieneweg reported that it was possible to compress enteric-coated pellets into tablets without significant damage using Eudragit L30 D-55 at 35% level and propylene glycol at 20% level as preferred plasticizers [4]. Lefranc et al. also reported similar findings for enteric-coated 5-ASA pellets [5]. Omeprazole is a member of acid-labile $H+K^+$-ATPase inhibitors also known as gastric proton pump inhibitors. Omeprazole is sensitive to heat, humidity, light, and organic solvents. Discoloration ranging from light beige to deep purple will occur immediately when omeprazole is exposed to unfavorable conditions. Stability of omeprazole for different pH values in solution was reported by Bailey

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et al. [6], Stability of commercial omeprazole products from 13 countries was reported by McCallum [7]. An in vitro evaluation, the degradation products for commercial omeprazole pellets were reported by Rodrigues [8]. A detailed list and chemical structure of omeprazole degradation products can be found in the USP or EP. The purpose of this study was to investigate the possibility of tableting enteric-coated omeprazole pellets using common tableting excipients, to study the accelerated stability of the tablets, and also to model omeprazole degradation based on the process and formulation factors.

## 2. Materials and methods

### 2.1. Materials

Omeprazole containing pellets were obtained by drug layering on sucrose–starch spheres a HPMC water-soluble film coating, and a final Eudragit L30 D-55 enteric coating was applied using a rotary fluidized-bed equipment based on a previously described method by Turkoglu et al. [9]. Coated pellets were sieved and a sieve fraction between 425 and 710 μm was used for further tablet manufacturing. Some common tablet excipients such as microcrystalline cellulose NF (Avicel PH 102, FMC, USA), pregelatinized starch (Starch 1500, Colorcon, USA), PEG 6000 (Merck, Germany), sodium carboxymethyl starch (Primojel, Generichem, USA) were used to design different tablet formulas containing 150 mg enteric-coated pellets corresponding to 20 mg omeprazole per tablet. Magnesium stearate was used as a lubricant in all formulations.

### 2.2. Wet granulation for excipients

To match the particle size of the excipients with the pellets a wet granulation process was carried out using Avicel and Starch 1500. Water was used as the binder and granules were dried overnight in a conventional oven at 45 °C, then the final product was sieved to collect granules with a size between 425 and 710 μm. The mixtures of enteric-coated pellets and the other excipients were formed in a laboratory size V-blender.

### 2.3. Tableting

Normal convex, 10 mm tablets with a target weight of 450 mg were compressed using a single-punch instrumented tablet press (Korsch EKO, Germany). Compression and ejection forces were monitored and recorded continuously using PC-based software (National Instruments, MAX, USA) and two force sensors (ICB Model 203B for upper punch and Model 201B03 for lower punch, PCB Piezotronics, New York, USA). Compression of tablets in an industrial type machine was performed using a 24-station rotary tablet press (GEA Courtoy R 190 FT, Belgium).

### 2.4. Tests for tablets

Tablet properties such as crushing strength (Holland C50, UK), friability, weight uniformity were checked and a gastro-resistance study was performed using the apparatus II of the USP 24 at 50 rev./min, in 0.1 N HCl at 37 °C for 2 h. A dissolution study (Sotax AT 7 Smart, Switzerland) was performed in pH 6.8 USP buffer for omeprazole release. A 10 ml sample was withdrawn from each dissolution beaker and then 2 ml of 0.25 N NaOH solution was added. The samples were filtered through a 45 μm filter and injected into the HPLC system as described in Table 1 assay method.

### 2.5. Stability testing protocol

The stabilities of five formulations and those of enteric-coated omeprazole pellets were studied under the accelerated conditions in 40 ± 2 °C and at 75% ± 5 RH in a humidiy cabinet (Binder 240, Germany), tablets and pellets were stored in brown glass bottles with a dessicant (S series), and without dessicant (F series) using rubber stoppers, and also in open containers (P series). During the stability test, the remaining omeprazole and the degradation products in tablets were followed at the first, second, and the third months using a stability-indicating HPLC method for omeprazole. Only the S series was analyzed for omeprazole and degradation products. A visual inspection was carried out for discoloration of tablets or pellets every day at the first week, and then once a week until the third month for all series (S, F, and P). A list of omeprazole impurities that were studied during the accelerated stability were: impurity A, 5-methoxy-1H-benzimidazole-2-thiol; impurity B, 5-methoxy-2-[[(4-methoxy-3,5-dimethypyridin-2-yl)methyl]-sulphanyl]-1H-benzimidazole; impurity C, 5-methoxy-2-[[(4-methoxy-3, 5-dimethypyridin-2-yl 1-oxide)methyl]sulphinyl]-1H-benzimidazole; impurity D, 5-methoxy-2-[[(4-methoxy-3, 5-dimethypyridin-2-yl)methyl]-sulphonyl]-1H-benzimidazole, 1-oxide; impurity G, 5-methoxy-2-[[(4-methoxy-3, 5-dimethypyridin-2-yl)methyl]-sulphonyl]-1H-benzimidazole.

Table 1
Summary of HPLC method for omeprazole assay and impurities

| | Assay method | Stability-indicating method |
|---|---|---|
| Column | Nova Pak $C_{18}$ 150 × 3.9 mm | Zorbax SB-PHENYL 250 × 4.6 mm, 5 μm |
| Flow rate | 1.0 ml/min | 1.2 ml/min |
| Injection volume | 20 μl | 30 μl |
| Column temperature | 35 °C | 35 °C |
| Wavelength | 280 nm | 280 nm |
| Mobile phase[a] | Buffer:ACN | Buffer:ACN |

[a] pH 6.0 USP phosphate buffer:acetonitrile (72:28).

### 2.6. Data analysis

For modeling the data to determine the effects of compression pressure and studied excipients on omeprazole degradation and tablet properties, artificial neural network software (STATISTICA Neural Networks, Release 4.0, USA) was used. The details of the artificial neural network (ANN) methodology can be found in the literature [10]. A three-way analysis of variance (ANOVA) was performed (SPSS 10.01 for Windows) as an example of traditional data analysis method and the results were compared with the ANN. Historical data were used for model forming including the five batches evaluated in accelerated stability study. The best network was reported based on the regression ratio, correlation coefficient, and the minimized error. As independent factors, tablet compression force, Avicel and Starch 1500 concentrations were used. The dependent variables included tablet crushing force and percent omeprazole degradation. The linear (LNN), multilayer perceptron (MLP), radial basis function (RBF), generalized regression (Genetic, GRNN) networks were considered. Three-dimensional response surfaces were constructed based on the model predicted values.

### 2.7. Analytical procedures and HPLC conditions

Two HPLC procedures were used. The first one was the assay procedure for omeprazole and the second method was the stability-indicating method for omeprazole. Both methods were fully validated before their routine use. Both HPLC procedures used the external standard method, and the area under the peak values were used for calculations. The validation tests included: system suitability, accuracy, reproducibility, linearity and ruggedness. The conditions are summarized in Table 1.

## 3. Results and discussion

### 3.1. Tablet properties

The five tablet formulations studied ($F_1$, $F_2$, $F_3$, $F_4$ and $F_5$) contained 150 mg of enteric-coated pellets that corresponded to 20 mg omeprazole in a 455 mg final tablet formula. Table 2 summarizes the composition of the formulas, and Table 3 shows the mechanical properties. Table 3 also includes additional data for an optimized batch ($F_4$) that was compressed using an industrial size rotary tablet press to compare the results with the single station tablet press. When physical tablet properties were considered, $F_4$ was found to be the best formulation with an average crushing strength value of 8.7 kg force and a friability value of less than 0.5%. $F_2$, $F_3$ and $F_5$ showed friability values more than 1% USP limit. Disintegration times for all formulations were less than 5 min.

Table 2
Prototype tablet formulations

| Formulation | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ |
|---|---|---|---|---|---|
| Pellet[a] | 150 | 150 | 150 | 150 | 150 |
| Avicel PH 102 | 150 | 100 | 150 | 270 | 150 |
| Starch 1500 | 70 | 50 | 120 | – | – |
| Primogel | 30 | 60 | 30 | 30 | 30 |
| PEG 6000 | 50 | 90 | – | – | 120 |
| Lubricant (%) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |

Average tablet weight: 455 mg ± 5%.
[a] Enteric-coated pellets containing 20 mg omeprazole per 150 mg pellet.

### 3.2. Percent dissolution and gastro-resistance

One of the most important properties of a modified release item is its resistance against gastric conditions. It is required that no more than 10% drug degradation would occur after 2 h in 0.1 N HCl solution. All formulations except $F_5$ complied with the condition. The best gastro-resistance was obtained with $F_4$ as 5% omeprazole degradation after 2 h using USP 24 Apparatus 2 at 50 rev./min and 37 °C. The free pellets showed no more than 1% degradation for omeprazole. Therefore the difference can be attributed to the tableting process and the effects of excipients. Percent dissolution data for tablets did not differ from free pellets since all formulations disintegrated freely in less than 5 min and at the 15th min, all the batches released at least 80% omeprazole and then drug release continued much more slowly. Fig. 1 shows the release profiles of five formulations without being exposed to HCl for 2 h and Fig. 2 shows the gastro-resistance of the formulations after being exposed to 0.1 N HCl solution for 2 h.

### 3.3. Scanning electron microscopy

Several scanning electron microscopy (SEM) photos were taken to obtain a visual assessment of the pellets under compression The SEM photos were taken by breaking a tablet in half. Fig. 3a shows a single enteric-coated pellet 700 μm in diameter protecting the integrity of the acrylate coating and embedded in the microcrystalline cellulose

Table 3
Some tablet properties

| Formulation | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_4^{\text{Rotary Press}}$ | $F_5$ |
|---|---|---|---|---|---|---|
| Tablet thickness (mm) | 5.92 | 5.79 | 5.52 | 5.63 | 4.69 | 5.73 |
| Crushing strength (N) | 63 | 54 | 52 | 90 | 85 | 65 |
| Friability (%) | 1.23 | 20 | 8 | 0.34 | 0.1 | 2.0 |
| Disintegration time (min) | 3 | 2.5 | 2 | 3 | 1.5 | 2 |

$F_4^{\text{Rotary Press}}$, batch size 11.000 tablets (Courtoy R 190 FT, 24-station rotary tablet press).

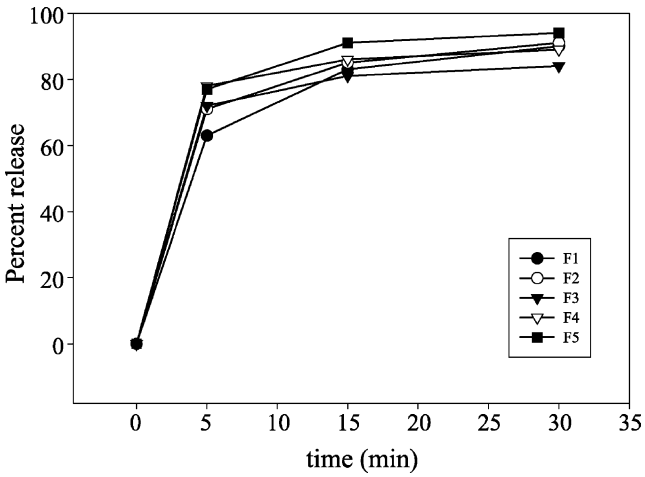


Fig. 1. Percent omeprazole release from tablets in phosphate buffer (pH 6.8) (USP 24 Paddle apparatus, 37 °C and 100 rev./min, acid phase was omitted).

matrix. Fig. 3b shows a cross-section of a tablet ($F_4$) containing individual pellets scattered inside a supporting matrix. One can observe the matrix deformation corresponding to a single pellet and there was no visible damage to the pellets. However, only damage to the enteric coating occured on the surface of the tablets. Granulation of the excipients to match the pellet size had a crucial role in absorbing the compression pressure. The Avicel matrix showed a strong plastic deformation and all the pellets inside a tablet maintained their shape with no significant change in their surface properties. We also agree that properly adjusting the tablet shape, having the smallest surface area/volume ratio, would result in better pellet protection as previously reported by Wagner et al. [3].

### 3.4. Stability of tablets

Stability studies were continued up to 90 days in a stability chamber at 40 °C and 75% RH free pellets were

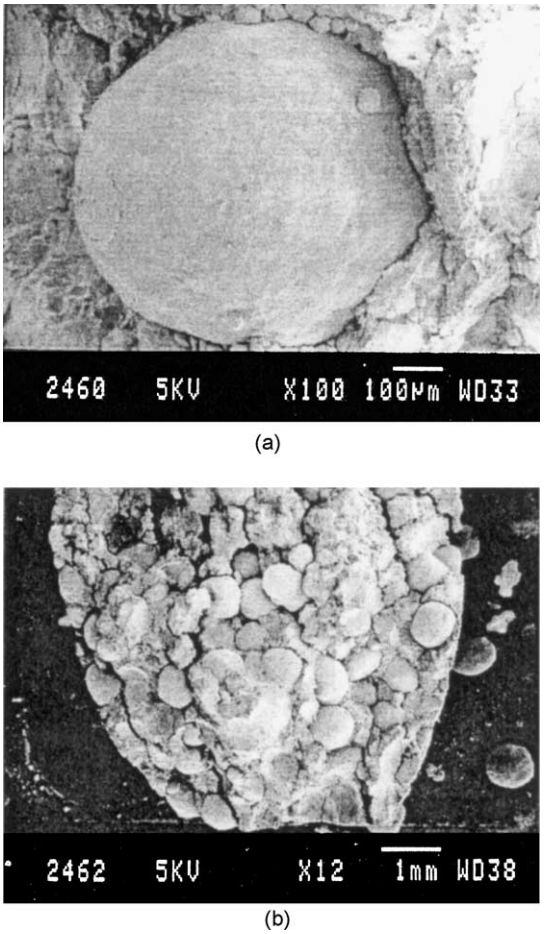


Fig. 3. (a) A single enteric-coated pellet inside the tablet matrix (pellet diameter, 650 μm). (b) Pellet distribution in the tablet matrix. Empty pellet nests (plastic deformation) and intact pellets inside the tablet are visible ($F_4$).

used as the control along with $F_1$, $F_2$, $F_3$, and $F_4$. Fig. 4 shows the remaining omeprazole vs time relative to the initial assay. None of the batches showed significant changes based on the ICH conditions such as a 5% potency

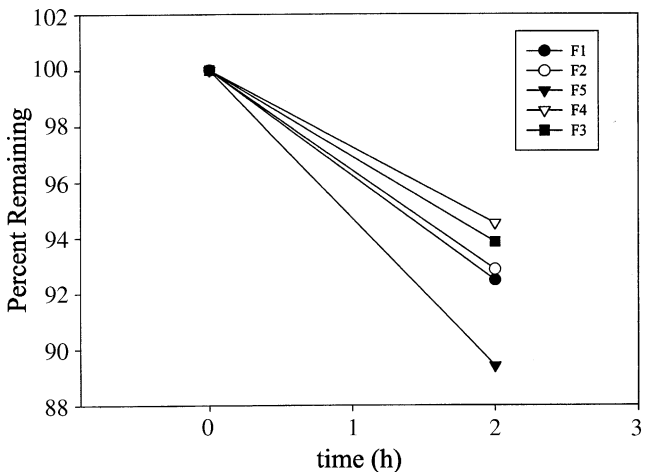


Fig. 2. Results of gastro-resistance test for tablets (2 h in 0.1 N HCl) (HPLC assay based on remaining omeprazole in tablets after 2 h).

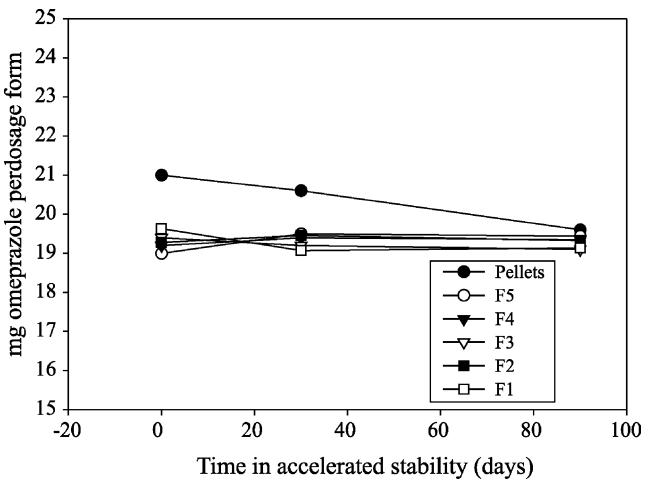


Fig. 4. Remaining omeprazole after 90 days in storage in tightly closed brown glass bottles with a dessicant.

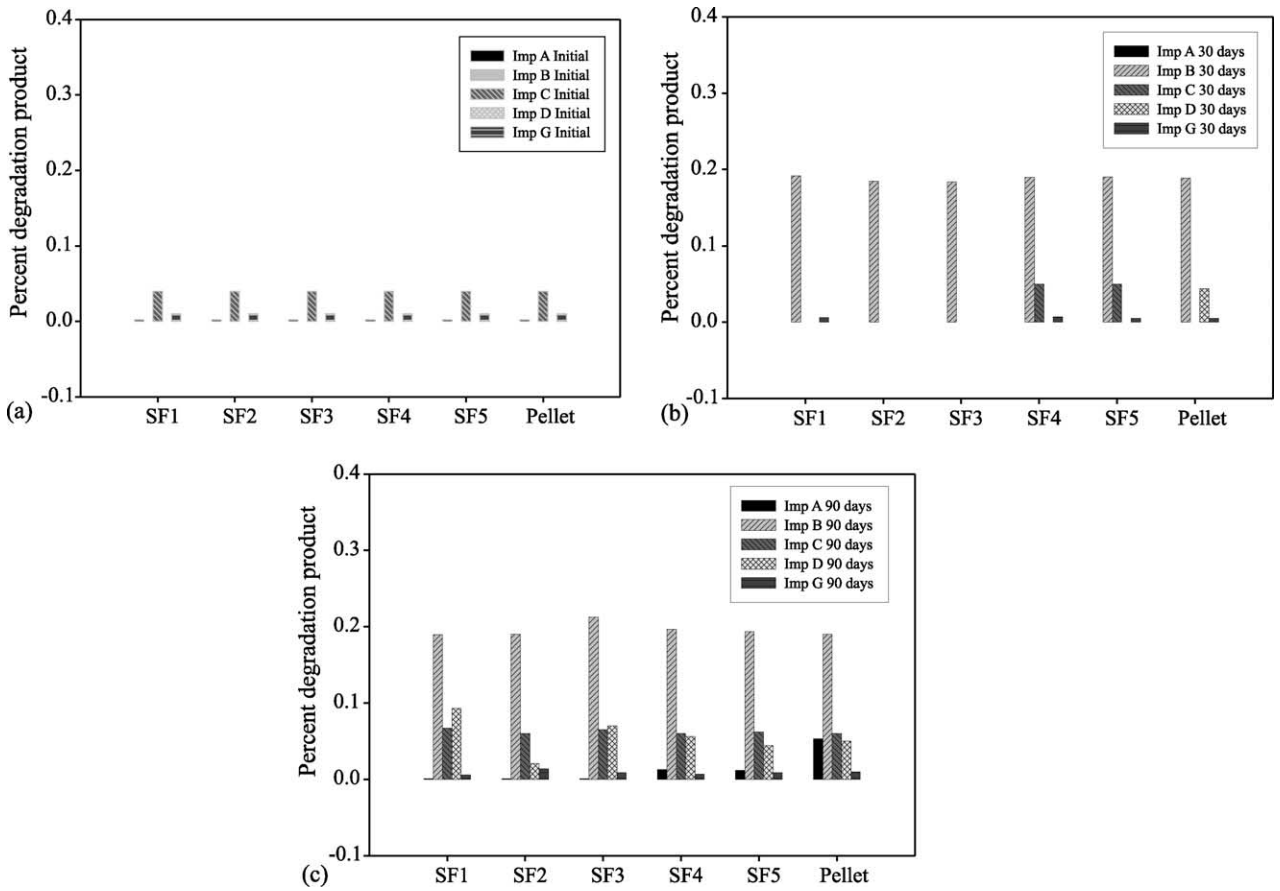


Fig. 5. (a) The initial impurity profile of formulations and the pellets based on the stability-indicating HPLC assay. (b) The 30th day impurity profile of formulations and the pellets based on the stability-indicating HPLC assay (40 °C, 75% RH). (c) Impurity profiles of formulations after 90 days in accelerated stability (40 °C, 75% RH) using the stability-indicating HPLC assay.

change from the initial assay or a specific degradant concentration exceeding the limits. All five tablet formulations showed acceptable stability in rubber-capped, brown glass bottles with a dessicant capsule. Fig. 5a–c shows the amount of omeprazole degradation products based on a stability-indicating HPLC assay at the initial, 30th and 90th day for the batches $SF_1$, $SF_2$, $SF_3$, $SF_4$, $SF_5$, and for the free pellets. The 'S' series were the ones that contained a dessicant capsule inside the brown bottles. Initially all the impurities were identical with the free pellets and the total amount was less than 0.05%. At 30 days, Imp B increased to 0.2% for all batches regardless of the formulation, however, it did not increase further even at 90 days. The 30 day graph showed some increase in Imp C for $SF_4$ and $SF_5$, and some increase in Imp D for free pellets. As can be seen in Fig. 5c, that is a summary of the 90th day assay, all five degradation products were visible for all the batches. Interestingly, Imp A did not form significantly in $SF_1$, $SF_2$, and $SF_3$, but occurred in $SF_4$, $SF_5$, and free pellets. This difference may be attributed to the presence of Starch 1500 in $F_1$, $F_2$, and $F_3$. Also $SF_2$ showed the smallest concentration of Imp D among all the batches.

The visual assessment of discoloration of tablet surfaces was also carried out up to 90 days. Fig. 6 shows the results. At the 90th day $SF_1$, $SF_2$, $SF_3$, $SF_4$, $SF_5$, and free pellets maintained white to light beige color as also expected from their HPLC assay. $SF_1$, $SF_2$, $SF_4$, and $SF_5$ did not show any discoloration until the 63rd day. However, the pellets in $SF_3$ started discoloration on the 35th day. Free pellets 'S' series showed the first sign of discoloration at the 63rd day exactly the same as the other formulas.

The formulations without a dessicant ($F_1$–$F_5$) and the pellets appeared as light beige to brownish at the 90th day, $F_1$ and $F_2$ being significantly darker. $F_1$, $F_4$ and $F_5$ showed first sign of discoloration at the 21st day, $F_2$ and $F_3$ at the 14th day. Free pellets 'F' series showed the first sign of discoloration at the 21st day. In this series of tablets, $F_1$ and $F_2$ showed inferior stability to the other formulas including the free pellets. Since all other factors were fixed, this faster discoloration was attributed to PEG 6000 in the formula. Hence, we concluded that PEG 6000 should have been excluded from an optimized formula containing omeprazole. In open containers, discoloration for all formulas was observed starting from the second day and reached a peak as dark brown at the third day.

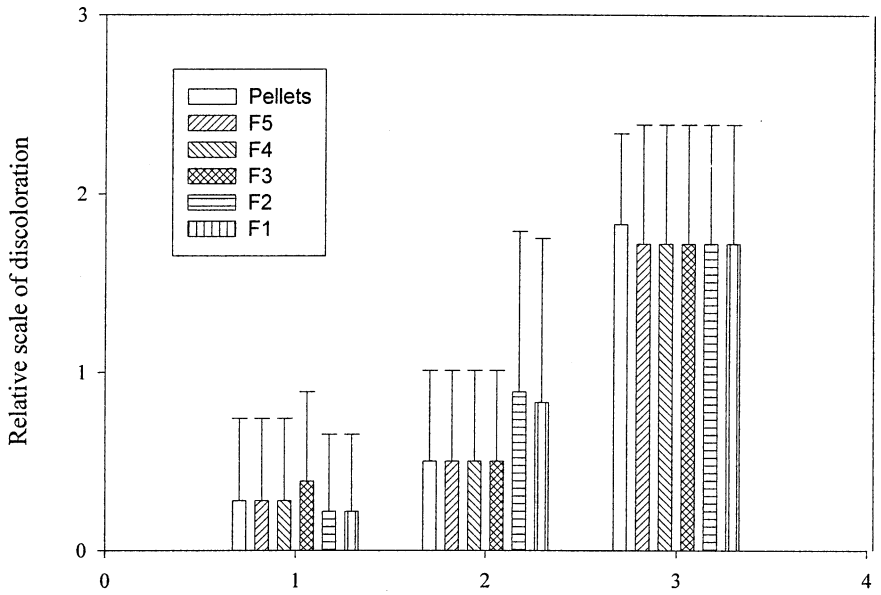


Fig. 6. Relative color change of five tablet formulations and pellets during accelerated stability test as 90th day with silicagel and without silicagel (1 and 2 on the *x*-axis) and the result for the third day for open containers (3 on the *x*-axis). (Color change on the *y*-axis: from white to deep purple).

### 3.5. ANN and ANOVA evaluation

One of the purposes of this study was to model the tablet crushing strength and percent omeprazole degradation in 0.1 N HCl which was used as an indicator of enteric coat damage based on the applied compression force, microcrystalline cellulose and pregelatinized starch concentration. Table 4 summarizes the experimental design which was a 20-experiment set containing three independent variables and two responses. The tablet crushing force which is a good indicator of a tablet's mechanical strength ranged between 11 and 363 N. Percent degradation values changed between 6.50 and 38% depending on the factor settings. Table 5 summarizes the ANN results. For the same data set a three-way analysis of variance (ANOVA) was performed as an example of traditional data analysis method and the results were compared with the ANN. Table 6 shows the results of ANOVA for tablet crushing strength and percent omeprazole degradation. For tablet crushing strength, a very good network performance was obtained which provided an opportunity for quantitative predictions with the MLP 3-10-1. For both responses out of 20 experiments, 10 training, 5 test, and 5 verification experiments were reserved. The network performance for percent degradation reported as good means one which can only withdraw qualitative conclusions. The RMS error terms for training, verification, and test were also reported in the table. Based on the best model estimates, 3D graphs were formed placing the responses on the *z*-axis and having the independent factors as the *x*- and *y*-axes. Percent omeprazole degradation in acid medium was found to be dependent on microcrystalline cellulose (Avicel granules) concentration. The relationship was curvi-linear, thus confirming the practical observations that microcrystalline cellulose granules absorbs all the compression energy and therefore protects the individual enteric-coated omeprazole pellets. Fig. 7a and b shows the 3D graphs. When the tablet crushing strength was evaluated based on the predicted responses, the mechanical properties of the tablets were the result of microcrystalline cellulose concentration and compresion force interaction as can be observed from

Table 4
Experimental design and list of observed and predicted responses based on the artificial neural network (ANN) system

| Case # | Force (kN) | Avicel | Starch | CS $(N)^O$ | CS $(N)^P$ | $\%D^O$ | $\%D^P$ |
|---|---|---|---|---|---|---|---|
| 1 | 4.9 | 150 | 0 | 56.54 | 47.43 | 13.07 | 14.08 |
| 2 | 9.8 | 150 | 0 | 104.17 | 143.28 | 24.11 | 15.29 |
| 3 | 4.9 | 300 | 0 | 134.94 | 130.24 | 26.13 | 25.23 |
| 4 | 9.8 | 300 | 0 | 209.42 | 287.04 | 12.42 | 10.96 |
| 5 | 4.9 | 0 | 150 | 11.07 | −0.1 | 26.13 | 23.37 |
| 6 | 9.8 | 0 | 150 | 16.37 | 5.39 | 37.75 | 39.17 |
| 7 | 4.9 | 0 | 300 | 14.99 | −4.31 | 20.19 | 19.94 |
| 8 | 9.8 | 0 | 300 | 43.41 | 28.91 | 27.83 | 35.01 |
| 9 | 4.9 | 50 | 50 | 29.11 | 40.47 | 22.8 | 19.60 |
| 10 | 9.8 | 50 | 50 | 51.65 | 63.21 | 29.59 | 29.80 |
| 11 | 4.9 | 100 | 100 | 72.23 | 106.62 | 13.66 | 13.81 |
| 12 | 9.8 | 100 | 100 | 126.13 | 184.63 | 14.77 | 16.52 |
| 13 | 4.9 | 60 | 60 | 66.64 | 53.90 | 7.07 | 18.26 |
| 14 | 9.8 | 60 | 60 | 93.79 | 88.10 | 6.48 | 26.94 |
| 15 | 4.9 | 150 | 50 | 90.85 | 116.62 | 12.75 | 15.98 |
| 16 | 9.8 | 150 | 50 | 236.87 | 227.46 | 9.94 | 11.99 |
| 17 | 4.9 | 150 | 0 | 62.03 | 47.43 | 23.91 | 18.97 |
| 18 | 9.8 | 300 | 0 | 344.67 | 287.04 | 13.86 | 10.96 |
| 19 | 4.9 | 300 | 25 | 162.97 | 166.11 | 9.55 | 23.50 |
| 20 | 9.8 | 300 | 25 | 360.93 | 348.68 | 9.29 | 8.91 |

O, observed; P, predicted; *%D*, percent omeprazole degradation; CS, tablet crushing strength (N).

Table 5
Summary table for artificial neural network (ANN) analysis for crushing strength and percent omeprazole degradation in accelerated stability

| | Tablet crushing strength | Percent degradation |
|---|---|---|
| Network type | MLP (3-10-1) | MLP (3-7-1) |
| Number of training cases | 10 | 10 |
| Number of verification cases | 5 | 5 |
| Number of test cases | 5 | 5 |
| Number of inputs | 3 | 3 |
| Number of hidden layers | 10 | 7 |
| RMS error | | |
| Training | 3.366 | 6.076 |
| Verification | 0.9148 | 3.788 |
| Test | 3.739 | 8.357 |
| Regression ratio | 0.1042 | 0.2742 |
| Correlation | 0.9947 | 0.9623 |
| Error | 0.9148 | 3.7880 |
| Network performance | Very good | Good |

MLP, multilayer perceptron. Inputs: tablet compression force, Avicel concentration, starch concentration; Outputs: crushing strength and percent omeprazole degradation.

the 3D graphs in Fig. 8a and b and this conclusion was also supported by the ANOVA procedure as the compression force ($P < 0.012$) and Avicel concentration ($P < 0.013$) terms were found to be significant. The 9.8 kN force–300 mg Avicel combination provided the strongest tablets, on the other hand 300 mg Avicel in combination with 4.9 kN resulted in intermediate tablet strengths. Starch 1500 concentrations were not found to be contributing to the tablet mechanical strength.

Overall, in this study it was found that enteric-coated omeprazole pellets could be compressed into quickly disintegrating tablets such as 20 mg omeprazole in 455 mg tablet as a single dosage form. When a certain size fraction of pellets was used such as 425–700 μm, the corresponding tablet excipients' size distribution was adjusted so that it approximated the pellets' size distribution for preventing segregation and assuring drug content uniformity. When compressing such systems the lubricant concentration like magnesium stearate must be kept at the minimum due to the low surface area. For instance in this study, 0.1% magnesium stearate was sufficient to be able to compress the tablets. The 90-day accelerated stability study in brown glass bottles with a dessicant capsule revealed that all five prototype formulations would result in an acceptable stability profile for both remaining omeprazole, and also for the increase of impurity concentrations. Although

Table 6
Three-way ANOVA for tablet crushing strength and omeprazole degradation

| Source | Type III SS | df | MS | $F$ | Sig. |
|---|---|---|---|---|---|
| *Dependent variable: crushing strength* | | | | | |
| Model | 4490.066 | 10 | 449.007 | 14.817 | 0.00 |
| Force | 287.467 | 1 | 287.467 | 9.486 | 0.01 |
| Avicel | 414.838 | 2 | 207.419 | 6.845 | 0.01 |
| Starch | 101.663 | 3 | 33.888 | 1.118 | 0.38 |
| Error | 303.043 | 10 | 30.304 | | |
| Total | 4793.109 | 20 | | | |
| $R^2 = 0.937$; $R^2_{adj} = 0.874$ | | | | | |
| *Dependent variable: omeprazole degradation* | | | | | |
| Model | 7665.737 | 10 | 766.574 | 24.873 | 0.00 |
| Force | 9.670 | 1 | 9.670 | 0.314 | 0.58 |
| Avicel | 236.939 | 2 | 118.470 | 3.844 | 0.05 |
| Starch | 238.909 | 3 | 79.636 | 2.584 | 0.11 |
| Error | 308.190 | 10 | 30.819 | | |
| Total | 7973.927 | 20 | | | |
| $R^2 = 0.961$; $R^2_{adj} = 0.923$ | | | | | |

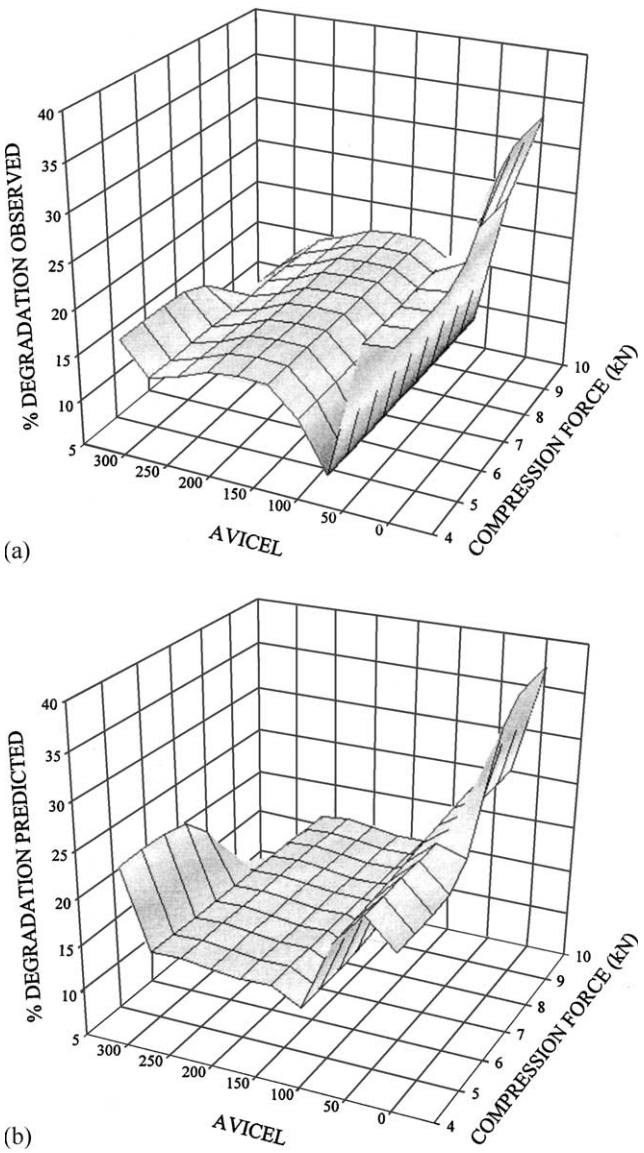


Fig. 7. (a) Percent omeprazole degradation vs Avicel and compression force. (b) Percent omeprazole degradation (ANN predicted) vs Avicel and compression force.

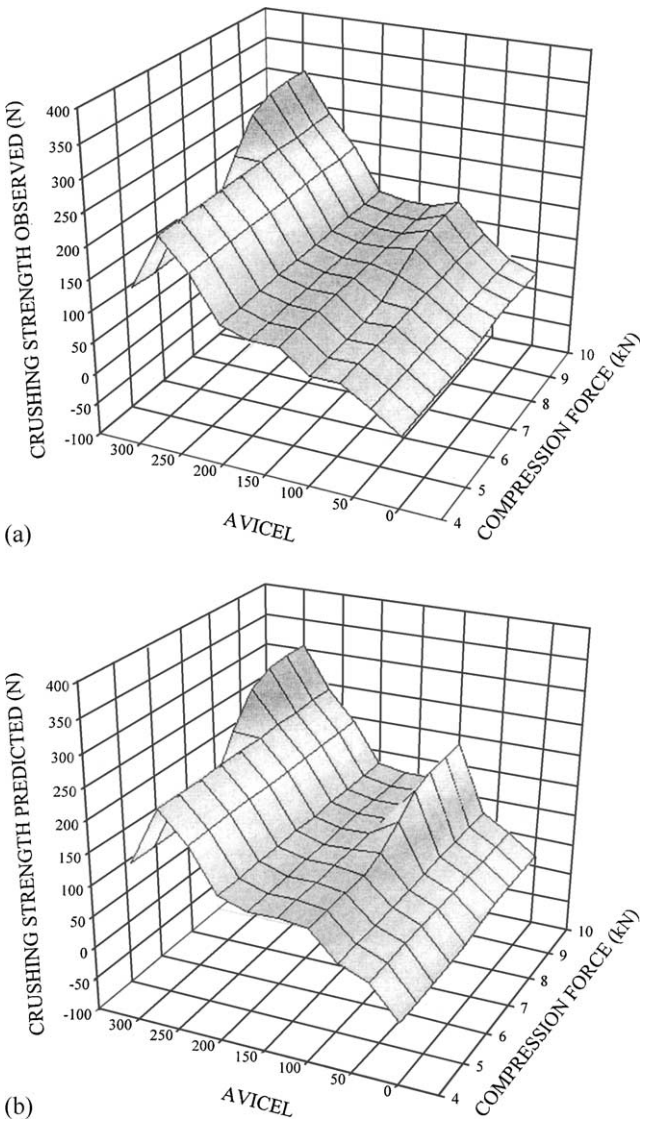


Fig. 8. (a) Tablet crushing strength vs Avicel and Compression Force. (b) Tablet crushing strength (ANN predicted) vs Avicel and Compression Force.

inclusion of Starch 1500 in the formulas adversly affected the mechanical properties of the tablets, it prevented formation of Imp D in the product. On the other hand, without using a dessicant capsule during the stability test $F_1$ and $F_2$ showed a faster discoloration than the $F_3$, $F_4$, and $F_5$ and it was attibuted to the presence of PEG 6000 in the formulas.

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