

OPTIMIZATION OF ASCORBIC ACID TABLET FORMULATIONS CONTAINING HYDROPHILIC POLYMERS

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Abstract

The aim of this study was to identify the most significant factors in the formulation of ascorbic acid tablets with hydrophilic polymers used as stabilizers against oxidative degradation. The study involved the use of a factorial experimental design with the use of regression analysis to derive equations in order to predict the optimum parameters in terms of tensile strength and release properties for the formulations.

The results have shown that pharmaceutical characteristics of ascorbic acid tablets are significantly affected by the polymer type and polymer concentration. The study also showed that ascorbic acid tablets with good mechanical, release and stability profiles could be obtained using hydrophilic polymers.

The study showed that with factorial experimental design and regression analysis, it is possible to derive regression equations and contour plots that allow the ranking of each variable according to its significance on the responses studied and hence with reduced time and experimental effort, it may be possible to predict if formulation composition will produce the desired response.

Rezumat

Scopul prezentului studiu a fost identificarea factorilor semnificativi pentru formularea optimă a comprimatelor cu acid ascorbic, utilizând polimeri hidrofilici ca agenți protectori împotriva degradării oxidative.

În acest sens s-a utilizat un model experimental factorial bazat pe metoda regresiei, în scopul optimizării proprietăților de cedare a substanțelor active din comprimate.

Keywords: ascorbic acid tablets; factorial design; hydrophilic polymers

Introduction

Ascorbic acid is a drug that is susceptible to oxidative degradation and, therefore, it requires significant physico-chemical and stability considerations in its formulation. Previous works showed the influence of hydrophilic polymers [1, 2] on the physico-chemical stability of ascorbic acid tablets. The studies showed that low viscosity hydrophilic polymers could be useful in stabilizing drugs which are susceptible to oxidation without significantly affecting the mechanical and release properties of such formulations. In the latter study [2], the compressional, tensile, release and stability profiles of the formulations of the tablets were evaluated and

Hydroxypropyl methylcellulose (HPMC) and a natural gum obtained from the incised trunk of *Khaya grandifolia* were found to give good mechanical, release and stability profiles for the ascorbic tablet formulations. This was achieved by dispersing the active ingredient in inert polymeric matrix [3]. Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance and have found wide application in the formulation of drugs [4, 5].

The present work seeks to optimize the formulations obtained from tablets containing Hydroxypropyl methylcellulose (HPMC) and Khaya gum with the intent of identifying and quantifying the specific factors responsible for the results observed and using of regression analysis postulate equations for the parameters evaluated [6, 7].

Materials and methods

The materials used were Ascorbic acid (Sigma, USA), Corn starch BP (Analar BDH, Poole, UK), Lactose BP (DMV Veghel, Netherlands), Hydroxypropylmethylcellulose (HPMC) (Colorcon Ltd., Dartford, Kent, UK) and Khaya gum (from *Khaya grandifoliola*) was collected from the Botanical Gardens, University of Ibadan, Nigeria.

Determination of the viscosity of polymers

Viscosities of aqueous solutions of the polymers (2% w/v) were determined at room temperature and 30rpm using Brookfield's viscometer (Brookfield ENG, Labs Inc, Stoughton, MA) (USP23–NF18, 1995)

Preparation of granules

Batches (200g) of ascorbic acid granules suitable for compression into matrix tablets were prepared using a modified form of the method proposed by Liu *et al.* Ascorbic acid was mixed in a planetary mixer with corn starch (5%w/w), lactose (10-20%w/w) and the polymers PEG 4000, PEG 6000, HEC, HPC, HPMC and Khaya gum (5 -25%w/w). While stirring, granulating fluid was added *via* a spray system. After the measured amount of water (approx. 20mL) was added, the wet granules were discharged manually through a number 12 mesh sieve (1400µm) and tray dried for 12hours at 50°C in a hot air oven, allowing minimum contact with air. The dried granules were passed through a number 16 mesh (1000µm) screen. The granules were then stored in air tight containers. The degree of mixing was determined by the U.V spectrophotometric assay of ascorbic acid at 260nm and was found to be >0.960. Fractions of 500 – 1000µm were separated and used for tablet optimization.

Preparation of tablets

Compacts were made on a Carver hydraulic hand press (model C, Carver, Inc., Menomonee Falls, WI, USA). Before each compression, the die and the flat faced punches (10.5mm) diameter were lubricated with talc. For each compact, 300mg of 500-1000 μ m size fraction of granules was weighed on an analytical balance, and filled into the die and compressed for one minute. After ejection, the tablets were stored over silica gel for 24 hours to allow hardening and elastic recovery. The relative density, D_0 of the tablets was calculated using the equation:

$$D = \frac{w}{v_t \rho_s} \quad (1)$$

where w is the weight of the tablet, v_t is the volume of the tablet in cm^3 and ρ_s is the particle density of the solid material in g/cm^3 .

Tablet crushing test

The load (N) required to diametrically break the tablet was determined at room temperature using a Monsanto hardness tester. Determinations were made in quintuplicate.

Disintegration test

Disintegration time for tablets was determined in distilled water at $37 \pm 0.5^\circ\text{C}$ in a BP Veego disintegration test unit (Veego, Mumbai, India). Six tablets were tested for each formulation. Tablets were considered to have disintegrated when all particles have passed through the wire mesh.

Dissolution Test

Drug release was determined using the USP apparatus II (Erweka Apparabetau, Germany) fitted with baskets rotated at 100rpm. The dissolution medium used was 900mL of distilled water at $37 \pm 0.5^\circ\text{C}$. 5mL samples were prelevated at time intervals and replaced with fresh dissolution medium. The amount of ascorbic acid dissolved was determined spectrophotometrically at 260nm, using filtered portions of the samples on a SP6-450 UV/VIS spectrophotometer (Pye Unicam, Middlesex, England).

Experimental design

Three independent process parameters (i.e., polymer type, polymer concentration and relative density) were chosen at two different levels (Table I). Table II summarizes the range of the three independent process parameters. A 2^3 full factorial design was used as a research methodology that required preparation of eight batches (Table II). The sequence of these experiments was randomized.

Table I

Independent process parameters and their levels

Independent Process Parameters	Associated variable	Lower Level (Coded -1)	Higher Level (Coded +1)
Polymer type	X ₁	HPMC	Khaya gum
Polymer concentration	X ₂	5% w/w	15%w/w
Relative density	X ₃	0.80	0.90

Table II

Factorial experimental design for ascorbic acid tablets incorporating HPMC and Khaya gum and values of tensile strength, disintegration and dissolution times (mins)

Batch No.	Polymer type Coded (X ₁)	Polymer concentration Coded (X ₂)	Relative density Coded (X ₃)	Tensile strength (MPa)	Disintegration time (min)	Dissolution time (t ₈₀)
1	-1	-1	-1	0.587	2.03	23.1
2	+1	-1	-1	0.303	3.12	32.7
3	-1	+1	-1	1.474	12.05	35.3
4	+1	+1	-1	0.854	12.75	44.5
5	-1	-1	+1	1.940	3.60	25.2
6	+1	-1	+1	0.485	6.41	37.2
7	-1	+1	+1	2.001	16.15	40.0
8	+1	+1	+1	1.014	14.21	47.1

-1: Low values; +1: High values

Apart from the factorial experimental design, the results obtained from this study were also subjected to a regression analysis using the MINITAB® Version 14.2 software, obtained from Minitab Inc. Pennsylvania, USA, which employs the least squares method to determine the statistical parameters of the data. The regression equation is an algebraic representation of the regression line and is used to describe the relationship between the response and predictor variables. The regression equation takes the form of:

Response = constant + coefficient (predictor) + ... + coefficient (predictor)

or $Y = b_0 + b_1X_1 + b_2X_2 + \dots + b_kX_k$

where Y was the response (crushing strength, disintegration time or dissolution time), and $b_0 \dots b_{22}$ were the regression coefficients.

Results and discussion

In order to determine the individual and interacting effects of the different formulation factors on the physicochemical properties of the tablets, a factorial experimental design was used. This has been found effective in determining the effect of various formulation factors on the characteristics of drug formulations [8, 9].

Three independent process parameters (i.e., polymer type, polymer concentration and relative density) were chosen at two different levels. Table II summarizes the range of the three independent process parameters. The purpose of using a full factorial experimental design was to conduct a comprehensive study of the effect of the process parameters and their interaction using suitable statistical tool.

The values of tensile strength, disintegration time and dissolution rate for the factorial experiments are given in Table II. These values are used in calculating the individual and interaction coefficients for the variables. The values of the individual and interaction coefficients are presented in Tables III and IV, respectively.

Table III

Summary of the individual coefficients of the variables on the tensile strength, disintegration time and dissolution time (t_{80}) of ascorbic acid matrix tablets containing HPMC and Khaya gum

Factor	Coefficient	Tensile strength (MPa)	Disintegration time(min)	Dissolution time (t_{80})
X_1	Effect	-0.418	0.333	4.737
	p-value	0.150	0.651	0.075
X_2	Effect	0.254	5.000	6.088
	p-value	0.240	0.069	0.059
X_3	Effect	0.278	1.303	1.738
	p-value	0.221	0.252	0.199

Table IV

Summary of Interaction coefficients of the variables on the tensile strength and dissolution time (t_{80}) of ascorbic acid tablets containing HPMC and Khaya gum

Factor	Coefficient	Tensile strength (MPa)	Disintegration time(min)	Dissolution time (t_{80})
X_1X_2	Effect	0.016	-0.643	-0.663
	p-value	0.896	0.448	0.448
X_1X_3	Effect	-0.192	-0.115	0.038
	p-value	0.307	0.868	0.958
X_2X_3	Effect	-0.106	0.088	0.088
	p-value	0.483	0.899	0.902

The individual and interaction effects provide an indication of the quantitative effects of the three variables studied on the tensile strength and release properties of the different ascorbic acid tablet formulations.

In the formulations incorporating HPMC and Khaya gum, all the coefficient values were positive except for the influence of polymer type which caused a decrease in the tensile strength. This indicates that HPMC had a higher binding property than the natural gum. The ranking of the coefficients was $X_1 > X_3 > X_2$ on TS, $X_2 > X_3 > X_1$ on DT and $X_2 > X_1 > X_3$ on t_{80} .

Polymer type was the most significant variable ($p < 0.05$) on tablet hardness, while both polymer type and concentration were the most influential variables on the release properties of the tablets.

For the interaction coefficients, the ranking tensile strength was $X_1X_3 > X_2X_3 > X_1X_2$, on disintegration time the ranking was $X_1X_2 > X_1X_3 > X_2X_3$; and on dissolution time $X_1X_2 > X_2X_3 > X_1X_3$. The results show that the interaction between polymer type and concentration (X_1X_2) had the most influential effect on the disintegration and dissolution times of the tablets, while the interaction between polymer type and relative density (X_1X_3) had the highest effect on tensile strength of the tablets.

On further analysis, combining all the variables with the inclusion of viscosity as a parameter to represent the type of polymer, yielded a model for each of the tablet properties considered. Thus separate equations were obtained for Tablet hardness (Y_1), Disintegration time (Y_2) and Dissolution time (Y_3), respectively (Equations 1-3). The predictors are also given as Viscosity (X_1), Polymer concentration (X_2) and Relative density (X_3). These options were considered and tested in order to obtain the best models for the formulation processes. The response and predictor variables used for the regression analysis to obtain an optimum formulation of ascorbic acid in terms of physicochemical stability are presented in Table V. These analyses were performed for the all the formulations as expressed in the factorial experimental design.

Table V
Response and predictor variables used for the regression analysis

Predictor (Independent variables) (X)	Response (Dependent variables) (Y)
Polymer type (X_1)	Tablet hardness (Y_1)
Polymer conc (X_2)	Disintegration time (Y_2)
Relative density (X_3)	Dissolution time (Y_3)

The models derived from the regression analysis are as follows:

$$Y_1 = 1.62 - 0.048 X_1 + 0.072 X_2 + 0.120 X_3 \quad (r = 0.984) \quad (1)$$

$$Y_2 = 9.90 - 0.063 X_1 + 5.00 X_2 + 1.30 X_3 \quad (r = 0.986) \quad (2)$$

$$Y_3 = 51.5 - 0.894 X_1 + 6.09 X_2 + 1.74 X_3 \quad (r = 0.994) \quad (3)$$

The high correlation coefficient ($r > 0.98$) obtained for all the relationships show how well the models can be used in predicting the mechanical and release properties of tablets incorporating the hydrophilic polymers. With these models, it will be possible to predict for any given set of materials or experimental conditions, the physicochemical properties of the resulting tablets. Conversely, where it is desired to obtain a product

with some known characteristics, the model can assist to determine the requirements in terms of materials and conditions [10].

The results obtained showed that for all the polymers studied, the most influential variable on the mechanical properties of the tablets was the concentration of polymer, while the polymer type had the highest influence on the release properties. Also, the factorial experimental design provided valuable insight into the influence of the various interactions between the various formulation factors on the responses studied [11]. For instance, the highest effect on the ascorbic acid tablet formulations generally was obtained from the interaction between polymer type and polymer concentration. This indicates that in selecting appropriate polymers in the formulation of tablets with the intent of exerting a protective effect with optimum release and mechanical properties, the most important decision is on the type of polymer to be incorporated and the quantity used in order to get the desired result. Values of polymer concentration and polymer type were coded and contour plots were established (Figures 1 - 3).

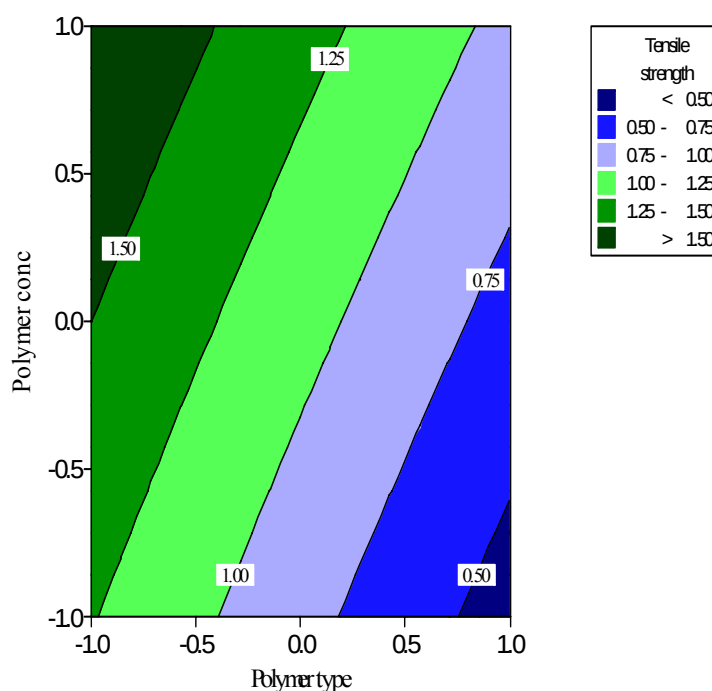
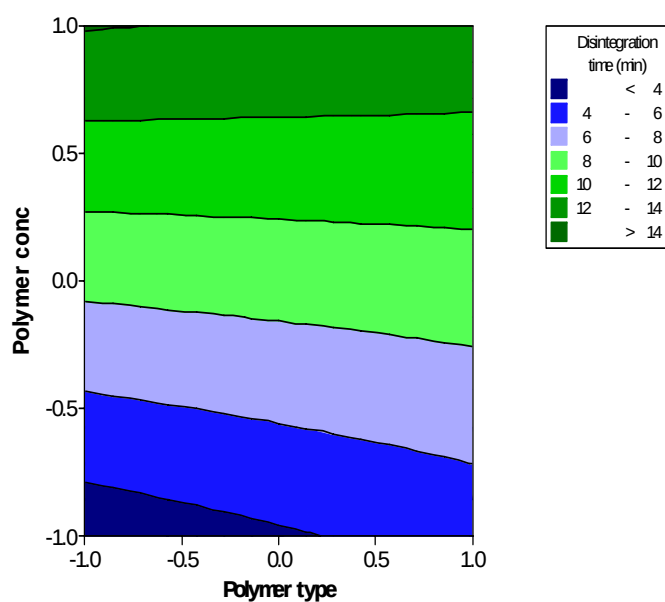
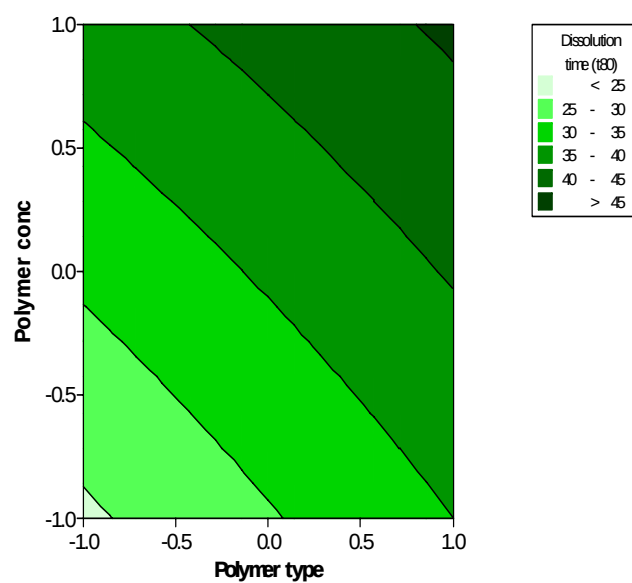


Figure 1

Contour plots of tensile strength of ascorbic acid tablets as a function of polymer type (HPMC and Khaya gum) and polymer concentration

**Figure 2**

Contour plots of disintegration time of ascorbic acid tablets as a function of polymer type (HPMC and Khaya gum) and polymer concentration

**Figure 3**

Contour plots of dissolution time (t_{80}) of ascorbic acid tablets as a function of polymer type (HPMC and Khaya gum) and polymer concentration

The variable, relative density, being least significant, was kept constant in drawing the contour plots. The contour plots showed very clearly the relationship between the independent variables and the responses. The developed contour plots are useful in predicting the relevant responses as they outline the relative effects of the variables. Figure 1 shows the influence of change in the concentration and polymer type on the tensile strength of formulations containing HPMC and Khaya gum. The relative influence of polymer concentration and type on the tablet strength of formulations containing either polymer are demonstrated by the dark green portion of the graph which shows that polymer concentration exerted a greater effect than polymer type on formulations containing either of these polymers. Similar contour plots for disintegration time and dissolution rate (Figures 2 and 3) show that polymer concentration has a higher influence on the release properties of the formulations than the polymer type.

The various results have confirmed that polymer type had a significant effect on the disintegration time and dissolution rates of the tablets, while polymer concentration was the most significant variable affecting both the strength and dissolution rates of the tablets. In summary, the results have shown that pharmaceutical characteristics of ascorbic acid tablets are significantly affected by the polymer type and polymer concentration. The study also showed that ascorbic acid tablets with good mechanical, release and stability profiles could be obtained using hydrophilic polymers.

Conclusion

The various results have confirmed that polymer type had a significant effect on the disintegration time and dissolution rates of the tablets, while polymer concentration was the most significant variable affecting both the strength and dissolution rates of the tablets. It is noteworthy that Khaya gum, a natural polymer obtained from the incised trunk of the plant *Khaya grandifoliola*, was found to give relatively comparable results with HPMC, a widely accepted synthetic polymer in the pharmaceutical industry. This suggests a good prospect for using this gum in the formulation of tablets with protective properties on the active ingredient.

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