Vol. 22 (2019) 45-51

# Formulation Development and Optimization of Taste Masked Generic Fast Dissolving Zinc Sulphate Tablets

E. M. MLUGU[1], P. TIBALINDA[3], R. SHEDAFA[3] AND E. KAALE[2,3*]

[1]*Department of Pharmaceutics and Pharmacy Practice, Muhimbili University of Health and Allied Sciences (MUHAS), Tanzania.*
[2]*Medicinal Chemistry Department, Muhimbili University of Health and Allied Sciences (MUHAS), Tanzania.*
[3]*Pharm R&D Laboratory, School of Pharmacy, Muhimbili University of Health and Allied Sciences (MUHAS). P.O Box 65013, Dar es Salaam, Tanzania.*

**Zinc sulphate tablets are indicated for the management of diarrhoea in children regardless of the cause. In Tanzania, there is only one pharmaceutical industry manufacturing zinc sulphate tablets and only 44% of children in need of zinc sulphate tablets get access to them. Fast-disintegrating tablets of zinc sulphate were prepared by direct-compression method after incorporating the superdisintegrant polyvinyl pyrollidine cross-linked. Different types of experiments and evaluation parameters for tablets were assessed. Design expert software version 7 was used to optimize the formulation. Tablets containing polyvinyl pyrollidine cross-linked showed excellent disintegration time, friability and hardness compared to formulations containing other superdisintegrants. Tablets with 30mg/60mg sodium saccharin/strawberry had a palatable taste. Assay was within 95% to 105%, disintegration time was less than 60 seconds, and hardness was between 3.0 kg/cm$^2$ to 4.0 kg/cm$^2$, which comply with official US Pharmacopeia requirements. Therefore, a taste masked generic formulation of 20 mg zinc sulphate fast dissolving tablets with accurate dose and palatable taste was successfully developed and optimized.**

**Key words:** Zinc sulphate monohydrate, Fast disintegrating tablets, Disintegration time.

## INTRODUCTION

Zinc is an essential micronutrient associated with metallo-enzymes and polyribosomes performing numerous biological functions including metabolism, cellular growth, and immune functions in humans [1]. Zinc deficiency has been identified as a common problem among children living in developing countries. It is known that children with marginal zinc deficiency in these countries are at increased risk of morbidity due to infectious diseases including diarrhoea.

Meta-analysis reviews demonstrated a beneficial effect of zinc administered to children less than 5 years during acute diarrhoea on stool output, diarrhoea duration, and proportion of episodes [2]. In 2004, WHO recommended all children with acute diarrhoea be treated with a zinc sulphate preparation (20 mg) for 10-14 days regardless of aetiology [3]. Effective implementation of these recommendations requires domestic pharmaceutical manufacturers, especially in developing countries, to develop zinc formulations which contain only zinc as an active ingredient [4]. In Tanzania there is only one pharmaceutical industry manufacturing zinc sulphate tablets. While diarrhoea continues to cause morbidity and mortality among children in Tanzania, less than 50% (44%) of children with acute diarrhoea have access to zinc sulphate preparations [5].

Despite the fact that the pharmaceutical industry is booming with new chemical entities, excipients, and new drug delivery systems, oral drug administration has been one of the most suitable delivery systems as it is non-invasive and widely accepted by patients for the delivery

*Author to whom correspondence may be addressed. Email: elia.kaale@gmail.com

of most drugs. Conventional oral drug delivery has been predominantly used for many years and various dosage forms like tablets, capsules and liquid preparations have been administered this route. Latest innovations for paediatric dosage forms include oral fast dissolving tablets, oral films and chewable tablets. Milk dissolving tablets are a recent drug delivery technology for pediatric use [6]. Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology.

Pharmaceutical development should consider ease of administration, palatability, appropriate excipients, stability and therapeutic equivalency of paediatric dosage forms. One of the important characteristics for paediatric formulation development is that the formulation should cover a broad age range because dosing due to the poor reproducibility of tablet breaking could compromise treatment efficiency [7]. In the case of zinc sulphate, 20 mg is the dose indicated for patients aged 6 months and above. Thus a developed formulation of 20 mg will cover a broad range of age.

## MATERIALS AND METHODS

### Equipment

The equipment used included a tubular mixer (Analytical Technology, Bangalore, India), a Korsh EK 02 tablet press machine (Korsch Pressen, Berlin, Germany), a Monsanto type tablet hardness tester (IEC, Mumbai, India), a Roche friabilator (Electro lab, Bangalore, India), a single pan balance (Shimadzu, AX200, Japan), a disintegration apparatus (Electrolab, Bangalore, India), graduated cylinders (Fisher Scientific, Schwerte, Germany), a sieve analyzer (Endicott's, Exeter, UK), glass bottles (Fisher Scientific, Schwerte, Germany), and ERWEKA TBH machine (ERWEKA GmbH, Heusenstamm, Germany).

### Materials

Zinc sulphate monohydrate, sodium saccharin, strawberry powder, sodium croscarmellose and sodium starch glycolate were gifts from Zenufa Laboratories (Dar es Salaam, Tanzania). Polyvinyl pyrollidine cross linked (PVP-CL), microcrystalline cellulose, water aerosil 200 (Shandong Liaocheng Ehua Medicine Co. Ltd., Shandong, China) and magnesium stearate (Hozhou Zhanwang Pharmaceutical Co. Ltd., Huzhou, China) were of pharmaceutical grade. EDTA (Carlo Erba Reagents, Spain), ammonium chloride (Loba chemie PVT Ltd. Mumbai, India), ammonia solution (Carlo Erba Reagents, Spain) and eriochrome T black (RFCL Limited, New Delhi, India) were of laboratory and analytical grades.

### Preparation of fast disintegrating zinc sulphate tablets

Tablets containing 20 mg equivalent to elemental Zinc were prepared using the direct compression method. The active pharmaceutical ingredient, diluents, disintegrant, sweetener and flavoring agent were weighed; hand sieved and mixed uniformly in a tubular mixer for ten minutes. The ingredients were mixed with the lubricants and punched using an EKO 2 single punch tableting machine with a concave punch.

### Selection of superdisintegrant

A set of benchmarking experiments were designed to obtain the disintegrant which could give best results in terms of friability, hardness, and disintegration time. Different disintegrants (PVP-CL, sodium starch glycolate and sodium crosscarmelose) were tested in order to obtain the best disintegrant with suitable variables. A total of nine batches, three batches each of sodium starch glycolate, PVP-CL and crosscarmelose sodium were formulated. The batches were tested for friability, hardness and disintegration time.

### Taste optimization and taste evaluation test

The aim of this phase was to get the minimum amount of sodium saccharin and strawberry that would be sufficient to mask the metallic taste of the drug. In this phase, experiments were designed to keep the amount of active ingredient and other excipients constant while varying the concentration of sodium saccharin and strawberry. Four batches were formulated and

tested for sweetness using organoleptic taste perception. The taste perception test was performed by six volunteers with their prior consent at the Pharmaceutical Research and Development Laboratory of the Muhimbili University of Health and Allied Sciences. The involvement of human volunteers in this study was ethically approved by the MUHAS Ethical board. To find a suitable concentration for the evaluation of the sweetness taste intensity during the comparative test, the perception and metallic taste recognition threshold of pure zinc sulphate was evaluated. To determine the threshold of metallic taste, a standard solution of pure zinc sulphate powder in distilled water was prepared as previously described [8]. The volunteers were then asked to taste 5 ml of solution by keeping it in their mouth for 5 seconds. Then, they were required to give one of these following perceptions:

1. "I detect a metallic taste".
2. "I detect an unpleasant taste but I cannot identify the taste",

The evaluation of tablet taste was carried out by dispersing a tablet of each batch in 10 ml of water to obtain 0.2% w/v zinc. The tablet batches were similar except for the amount of sweetener and flavor. The test was performed on the dissolved samples instead of the solid samples to reduce the wide variability of drug concentration in the mouth resulting from different salivation conditions between volunteers occurring when a solid sample is used. Volunteers were blinded for the concentration of sweetener and flavor to avoid bias. The volunteers were asked to taste 5 ml of each sample as previously described and leave the sample in the mouth for five seconds. A wash out period of 3 min after each sample was used where volunteers rinsed the mouth with clean water. After the test they were required to tell which sample had the most pleasant taste without metallic aftertaste and results were recorded.

**Formulation optimization by design of experiment**

D-optimal mixture design was used to evaluate the effect of changes in mixture compositions on dependent variables and statistical optimization of the formulation with the least number of experiments. D- Optimal designs are straight optimizations based on chosen optimality criterion and the model that will be fitted. Both process and mixture can be optimized by this method [9]. Tablets were prepared using constant active ingredient proportion (16.6%), magnesium stearate (0.9%), aerosil (0.5%), sodium saccharin (12%) and strawberry flavor (15%). Thus the experimental range lay between 0 and 55% w/w. Constrains were applied based on applicable amounts of the components in pharmaceutical formulations. Tablet hardness, disintegration time and friability were considered as dependent variables.

**RESULTS**

In disintegrant selection, three strengths of each of the disintegrants used were selected. It was observed that formulations with a concentration of 32.5 mg of each of the three disintegrants tested were the best in terms of disintegration time, hardness and friability (batch 2, 5 and 8) (Table 1). However, in further experiments it was observed that formulations with PVP-CL were superior in terms of friability, disintegration time and hardness. In the test of palatability five of the six volunteers detected the batch with 30mg and 60mg of sodium saccharin and strawberry flavour, respectively, as the pleasant tasting batch (Table 2).

**Analysis of mixture data for optimization**

Thirteen corresponding runs of experimental plan in which the mixture component proportions were varied were obtained (Table 3). Based on statistical analysis (analysis of variance; ANOVA) a cubic model was chosen for modeling the results from the D-optimal design for disintegration time and friability. For the hardness response, the linear model was fitted to the data ($p<0.05$) (Table 4). The mathematical models generated for the responses are as follows:

$$\mathbf{Y_1} = 1.46498X_1 - 2.5X_2$$

$\mathbf{Y_2}$ = $12.03X_1 - 772.8X_2 + 1373.1X_1X_2 - 777.3X_1X_2 \times (X_1 - X_2)$

$\mathbf{Y_3}$ = $37.7X_1 - 2395.8X_2 + 77.2X_1X_2 - 0.79X_1X_2 \times (X_1 - X_2)$.

Where

$Y_1$ = hardness, $Y_2$ = disintegration time, $Y_3$ = friability, $X_1$ = Microcrystalline cellulose, $X_2$ = PVP-CL.

**Table 1: Formulation trials for disintegrant selection**

| Ingredients (mg) | Batch Code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **B1** | **B2** | **B3** | **B4** | **B5** | **B6** | **B7** | **B8** | **B9** |
| Zinc Sulfate Monohydrate | 54.9 | 54.9 | 54.9 | 54.9 | 54.9 | 54.9 | 54.9 | 54.9 | 54.9 |
| Sodium CMC-CL | 16.3 | 32.5 | 48.8 | - | - | - | - | - | - |
| PVP-CL | - | - | - | 16.3 | 32.5 | 48.8 | - | - | - |
| Sodium Starch Glycolate | - | - | - | - | - | - | 16.3 | 32.5 | 48.8 |
| Microcrystalline Cellulose | 162.5 | 146.3 | 130.0 | 162.5 | 146.3 | 130.0 | 162.5 | 146.3 | 130.0 |
| Strawberry Powder | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 |
| Sodium Saccharine | 31.0 | 31.0 | 31.0 | 31.0 | 31.0 | 31.0 | 31.0 | 31.0 | 31.0 |
| Aerosil | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 |
| Magnesium Stearate | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 |
| **Total** | **330** | **330** | **330** | **330** | **330** | **330** | **330** | **330** | **330** |

**Table 2: Organoleptic test results for various compositions of sodium saccharin/strawberry favour**

| CASE | COMPOSITION1 (20/60mg/tab) | COMPOSITION2 (30/60mg/tab) | COMPOSITION3 (40/60mg/tab) | COMPOSITION3 (60/60mg/tab) |
|---|---|---|---|---|
| 01 | 0 | 0 | 1 | 0 |
| 02 | 0 | 1 | 0 | 0 |
| 03 | 0 | 1 | 0 | 0 |
| 04 | 0 | 1 | 0 | 0 |
| 05 | 0 | 1 | 0 | 0 |
| 06 | 0 | 1 | 0 | 0 |

Key: 0 = participant did not select the composition as palatable; 1 = participant selected the composition as palatable.

**Table 3: Experimental plan for the D-optimal design and results**

| Run | Variable factors (%) | | Response | | |
|---|---|---|---|---|---|
| | **Microcrystalline cellulose (X1)** | **PVP-CL (X2)** | **Disintegration time** (s) | **Friability** (%) | **Hardness** ($kg/cm^2$) |
| 1 | 40.00 | 15.00 | 12.00 | 0.30 | 2.17 |
| 2 | 46.22 | 8.78 | 16.00 | 0.23 | 4.20 |
| 3 | 40.00 | 15.00 | 12.00 | 0.30 | 2.17 |
| 4 | 40.00 | 15.00 | 12.00 | 0.30 | 2.17 |
| 5 | 5.00 | 5.00 | 300.00 | 1.70 | 6.15 |
| 6 | 42.52 | 12.48 | 15.00 | 0.15 | 3.02 |
| 7 | 50.00 | 5.00 | 300.00 | 1.70 | 6.15 |
| 8 | 50.00 | 5.00 | 300.00 | 1.70 | 6.15 |
| 9 | 45.00 | 10.00 | 15.00 | 0.13 | 4.05 |
| 10 | 41.26 | 13.74 | 13.00 | 0.20 | 2.57 |
| 11 | 48.74 | 6.26 | 56.00 | 0.10 | 5.92 |
| 12 | 47.48 | 7.52 | 28.00 | 0.09 | 5.50 |
| 13 | 45.00 | 10.00 | 15.00 | 0.13 | 4.05 |

**Table 4: Analysis of variance table (ANOVA) of dependent variables**

| Sources of variation | Sum of Squares | Df | Mean Square | F | p-value |
|---|---|---|---|---|---|
| **Hardness** | | | | | |
| Model | 3075.18 | 1 | 3075.18 | 753.65 | < 0.0001 |
| LinearMixture | 3075.18 | 1 | 3075.18 | 753.65 | < 0.0001 |
| Residual | 44.88 | 11 | 4.08 | | |
| Lack of Fit | 44.88 | 6 | | | |
| Adj R-Squared | 0.9843 | | | | |
| **Friability** | | | | | |
| Model | 4.80 | 3 | 1.60 | 28.23 | < 0.0001 |
| Linear Mixture | 2.11 | 1 | 2.11 | 37.22 | 0.0002 |
| X1X2 | 1.84 | 1 | 1.84 | 32.56 | 0.0003 |
| X1X1(X1-X2) | 0.59 | 1 | 0.59 | 10.38 | 0.0104 |
| Residual | 0.51 | 9 | 0.057 | | |
| Lack of Fit | 0.51 | 4 | 0.13 | | |
| Adj R-Squared | 0.8719 | | | | |
| **Disintegration time** | | | | | |
| Model | 1.762E+005 | 3 | 58740.17 | 73.76 | < 0.0001 |
| Linear Mixture | 1.024E+005 | 1 | 1.024E+005 | 128.58 | < 0.0001 |
| X1X2 | 4967.34 | 1 | 49767.34 | 62.49 | < 0.0001 |
| X1X2(X1-X2) | 16927.92 | 1 | 16927.92 | 21.26 | 0.0013 |
| Residual | 7167.18 | 9 | 796.35 | | |
| Lack of Fit | 7167.18 | 4 | 1791.80 | | |
| Adj R-Squared | 0.9479 | | | | |

**Formulation optimization**

In the design, the points with higher desirability were the best options to obtain tablets with suitable properties. Four formulations with high desirability (>50%) were suggested in this procedure (Figure 1). The two with desirability of 100% and 75.6%, respectively, were prepared and analysed for friability, disintegration time and hardness.

The optimized formulation with desirability of 100% was finally selected as the optimal formulation for further experiments. The selection was based the desirable physical characteristics as well as good correlation between predicted and observed results for all responses (Table 5).

**Table 5: Validation step: optimized levels for independent variables and comparative values of predicted and observed responses for numerically optimized formulations.**

| Desirability | Variable factor (%) | | Response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | AVICEL (X1) | PVP-CL (X2) | Hardness ($kg/cm^2$) | | Disintegration time (s) | | Friability(%) | |
| | | | Pred. | Obs. | Pred | Obs. | Pred. | Obs. |
| 100% | 45 | 10 | 3.3 | 3.5±0.2 | 16 | 20.23±3.32 | 0.1 | 0.04 |
| 75% | 46.2 | 8.8 | 4.2 | 4.6±0.7 | 18 | 30±4.21 | 0.2 | 0.045 |

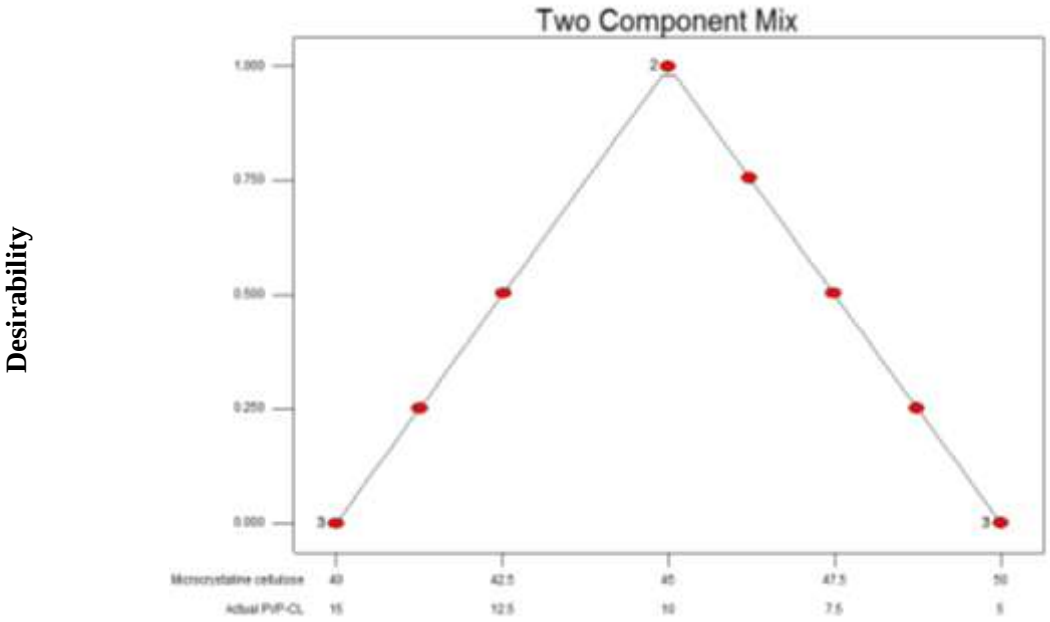


**Figure 1: Desirability profile for optimization procedure**

**Evaluation of fast disintegrating tablets for the optimal formulation**

The optimized formulation was evaluated for assay, disintegration time, friability and hardness and all the parameters were within the acceptable range according to USP. All dispersible zinc sulphate tablets prepared for the optimized batch were found to contain zinc sulphate within 98±2.15% of the label claim. Hardness of the tablets was in the range 3.5 ± 0.50kg/cm$^2$. Percentage weight loss in the friability test was less than 0.05% in all cases. Tablets formulated disintegrated rapidly within 20.53 ± 3.32 (15-25) seconds.

## DISCUSSION

The present study reports a developed and optimized formulation of fast disintegrating zinc sulphate tablets with palatable taste prepared by the direct compression technique. In this formulation the selection of the best disintegrant and optimization of the disintegrant and binder were successively achieved.

One of the most important parameters in fast disintegrating tablets is the disintegration time. PVP-CL was the best disintegrant with the desirable outcome variable among the three superdisintegrants used in this study. This may be due to the fact that this superdisintegrant disintegrates by wicking through capillary action and fibrous structure which gives minimum gelling leading to a short disintegration time as compared to the other two superdisintegrants whose mechanism of disintegration involves swelling leading to longer wetting time. These results are similar to a study which compared the disintegration time between sodium starch glycolate and PVP-CL in the formulation of valsartan fast disintegrating tablets [10].

Sodium saccharin was used as sweetener in this formulation. Although it is a suitable artificial sweetener, it may have an unpleasant after taste when used in higher concentration in formulations [11]. Strawberry flavour was combined with sodium saccharin to avoid using higher concentrations of sodium saccharin. The formulation was optimized and the balanced concentrations between the two were obtained. In the pleasant taste experiment a majority of volunteers detected the batch with an intermediate amount of saccharin as the most pleasant preparation.

The defined target for disintegration time, friability and hardness was achieved simultaneously with respect to predefined constraints by D-optimal mixture design.

Suitable balancing between the levels of components is essential to acquire tablets with optimal physical properties. At this stage, the defined desirable areas of three responses were superimposed and the region of interest was generated. The optimal formulation was best predicted by the design. The tablets obtained were of good quality with regard to drug content, friability, hardness and disintegration time. The chosen formulation fulfilled the USP specifications for fast disintegration tablets.

## CONCLUSION

Fast disintegrating zinc sulphate tablet formulation was successfully developed and optimized for disintegrating time, friability and hardness. Optimization procedure was facilitated using D-optimal mixture design. Physicochemical characteristics of the optimized formulation met all pharmaceutical requirements according to the USP. In this study PVP-CL was the best disintegrant. The formulation may be scaled up and adopted for commercial production.

## ACKNOWLEDGEMENT

We convey our sincere thanks to Zenufa Laboratories for supplying raw materials. We also thank all volunteers for the pleasant taste experiment. Our thanks and appreciation go to all staff in the Pharm R&D Laboratory at MUHAS for their tireless support.

## REFERENCES

[1] C. Hotz and K.H Brown. Food Nutr. Bull. 25, 2004, S91-S204.

[2] B. Patro, D. Golicki and H. Szajewska. J. Aliment. Pharmacol. Ther. 28, 2008, 713-723.

[3] World Health Organization and United Nations Children's Fund. WHO /UNICEF Joint statement: Clinical management of acute diarrhoea. WHO, Geneva, 2004.

[4] World Health Organization. Production of zinc tablets and zinc Oral Solutions. Guidelines for program managers and pharmaceutical manufacturers. WHO, Geneva, 2009.

[5] Ministry of Health and Social Welfare. Tanzania Demographic and Health Survey. Calverton 2011.

[6] S. Butani, H. Shah and D. Parikh. Int. J. Drug Form. Res. 5, 2014, 84-96.

[7] P.K. Raju and P.Srinivas. Int. J. Drug Form. Res. 1, 2010, 58-79.

[8] Y. Shahzad, S.Nisar, H. Shah, S. Atique, M.T. Ansari and F. Bashir. Brazilian J. Pharm. Sci. 47, 2011, 323-330.

[9] C.P. Jain and P.S. Naruka. Int. J. Pharm. Pharm. Sci. 1, 2009, 219-226.

[10] Y. Fu, S. Yang, S.H. Jeong, S. Kimura and K. Park . Crit. Rev. Ther. Drug Carrier Syst. 21, 2004, 433-475.

[11] R.C. Rowe, P.J. Sheskey and S.C. Owen. Handbook of Pharmaceutical excipients, 5th edition. Pharmaceutical Press, London. 2006, p. 641.