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FINAL REPORT ON

THE FORMULATION OF A TABLET ALTERNATIVE FOR HOME ORAL REHYDRATION THERAPY IN TROPICAL CLIMATES

Submitted to

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Submitted by

Charles R. Drew University of Medicine and Science,

International Health Institute

Dr. Rosalyn C. King, Principal Investigator

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ABSTRACT

Oral rehydration therapy (ORT) is recognized in the international health community as a cost-effective means of providing electrolyte replenishment in diarrheal diseases, and reducing infant and child mortality from dehydration caused by diarrheal diseases. The therapy consists of the intake of an oral rehydration salts (ORS) solution, a simple mixture of electrolytes and glucose added to water.

The purpose of this study is to prepare and evaluate standard and alternative ORS formulations as a preliminary step to developing a suitable ORS tablet alternative for enhanced shelf-life, increased accuracy, and economy for routine home use in ORT in developing countries. The study was conducted between October, 1985 and May, 1987. The research methods and procedures involved the use of approximately 20 different chemicals and substances, the preparation of binders (using cornstarch), and the preparation and testing of tablets. Tests for the following properties were performed on the granules: bulk density, granule density, porosity, flow rate, and friability. The evaluation of the physical properties of the tablets included tests of weight, porosity, thickness, dissolution time, and friability. Chemical analysis in conformance with the U.S Pharmacopeia XXI and stipulated by protocol and stability tests were performed on all formulations.

The study results indicate that no single group emerges as an outstanding candidate for a tablet formulation; however, none

could be ruled unsuitable. The tablets prepared in this study lack the requisite dissolution speed and clarity of resulting solution, both of prime importance for increased patient compliance. Formulation of a tablet alternative for home ORT is promising because all existing problems are solvable; however, more long-term experiments need to be performed to make conclusive statements and before a suitable tablet can be developed.

1. INTRODUCTION

The high vulnerability of infants and children under the age of 5 to disease is evidenced in the high proportion of deaths (more than half of all in developing countries) that occur during the first year of life. One of the most frequent causes of premature death in infants and children in developing countries is dehydration from diarrheal disease. Adults and older children in these countries are also at high risk of serious illness an death from diarrheal disease.

ORT is recognized by A.I.D. as a proven, cost-effective technology for reducing infant and child deaths form diarrheal disease. ORS, a simple mixture of electrolytes and glucose, is acknowledged as the best treatment today available to treat diarrheal disease. Presently , the therapy consists of the intake of large quantities of water containing various salts. However, massive effort is required to overcome problems of social acceptance, financing, and the logistics of supplying ORS to target populations in developing countries. To this end, this study was undertaken.

The World Health Organization (WHO) recommends a standard formula for oral rehydration salts (ORS). The widely used WHO preparation is a powder formulation of salts and glucose in definite quantities dissolved in a liter of water and taken orally.

The purpose of this study is to prepare and evaluate standard and alternative ORS formulations as a preliminary step to developing a suitable ORS tablet for enhanced shelf-life,

increased accuracy, and economy for routine home use in ORT in developing countries. The focus of this study is to alleviate problems that exist with the WHO glucose-electrolyte formulation. One problem is that the liter of water containing the salts must be discarded 24 hours after being prepared due to the increased likelihood of bacterial contaminant growth. It was thus proposed that the use of a unit dosage form would be more suitable. Therefore, a tablet form would be ideal as it would allow greater quantitative precision for home use, promote patient compliance, and increase the stability of the product. Tablets were thus made using the WHO formulation and certain variations with the aim of improving the stability and acceptability of the preparation.

The three general methods of tablet preparation are (1) direct compression, (2) wet granulation, and (3) dry granulation. Selection of the method of preparation is based on the ingredients added such that the tablet formulation attains the desired physical characteristics and can be rapidly compressed into tablets. After compression, the tablets must conform to a number of characteristic attributes such as appearance, hardness, disintegration ability, and uniformity. Most of these attributes, except uniformity, do not have fixed standards because all are influenced by the method of preparation, the size of the tablets prepared, and the materials present in the formulation.

The next sections describe the work done. The scope of the studies performed are in accordance with the proposal funded by the U.S. Agency for International Development (A.I.D.) (Grant No. DAN-5053-G-SS-5074-00).

2. BACKGROUND ON ORAL REHYDRATION SALT FORMULATIONS

The following WHO ORS powder formulations (WHO and UNICEF 1984) are dissolved in 1 liter of water for oral administration to dehydrated patients suffering from diarrheal diseases:

ORS bicarbonate (original)	GRAMS
Ingredients	
Sodium chloride	3.5
Sodium bicarbonate	2.5
Potassium chloride	1.5
Glucose anhydrous	20.0

ORS citrate (new)	GRAMS
Ingredients	
Sodium chloride	3.5
Sodium citrate	2.9
Potassium chloride	1.5
Glucose anhydrous	20.0

When properly stored, the shelf-life of the ORS packets is reported to be up to 3 years from the date of manufacture if packaged in aluminum laminate or an equivalent material.

The ORS citrate/glucose formulation is the product presently recommended by WHO and supplied by the United Nations Children's Emergency Fund (UNICEF). However, the ORS bicarbonate/glucose formula has been used successfully for rehydration in diarrheal disease in developing countries for may years. In current packaging, the bicarbonate formulation ages more rapidly than does

the citrate/glucose powder (Siewert and Gnekow 1983). Unfortunately, little appears in the scientific literature on the stability of ORS formulations or on clinical or shelf-like evaluations of ORS tablet formulations.

The literature is replete with reports on the experience of various developing countries with both WHO-recommended ORS and home-made sugar/salt solutions, as well as with examples of glucose substitutes, such as sucrose (Moenginah et al. 1975; Nalin 1975; Nalin et al. 1978; Palmer et al. 1977; Sack et al. 1980) and starches or amino acids (Molla et al. 1982; Patra et al. 1982, 1984; Greenough 1983; Mahalanabis and Patra 1983). The amino acid glycine, for example, was found to support sodium and water absorption in a manner similar to that of glucose (Nalin et al. 1970; Rhode and Cash 1973). One study comparing the WHO ORS bicarbonate formula plus glycine found significantly lower stool volume, shorter duration of diarrhea, and less total ORS required among the children receiving this treatment (Patra et al. 1984). In another study using cooked rice powder mixed with WHO/UNICEF ORS salt minus glucose, the rice-powder-based ORS was better accepted by the patients and resulted in reduced fluid losses and shortened durations of diarrhea (Molla et al. 1982; Patra et al. 1982). Based on the aforementioned studies of Molla & Patra, Greenough (1983) proposed packaging or tabletting only the salts (excluding the glucose) and using these in cereal based soups for added contribution to the nutritional status during ORT.

During 1984, WHO recommended a change in the complete ORS

formula by simple replacing sodium bicarbonate (baking soda) with sodium citrate (trisodium citrate dihydrate) (WHO and UNICEF 1984). Three studies, involving adults and older children (aged 5 and above) with cholera, showed stool volume to be 26 to 46 percent less with the sodium citrate formula (Program for Appropriate Technology in Health 1980). A special study evaluated sodium acetate as a substitute for bicarbonate and concluded that sodium acetate could be substituted for bicarbonate in the original WHO ORS formula without adversely affecting either the palatability or clinical efficacy (Patra et al. 1982). A second group studied the solid-state stability of ORS and concluded that the glucose component decomposes more rapidly in the presence of bicarbonate when stored at 50 deg C and with high humidity (Izgu et al. 1981). Researchers for WHO found the ORS citrate formulation to be more stable than the ORS bicarbonate powder (Siewert and Gnekow 1983).

UNICEF has provided ORS packets for many ORT programs and during 1984 was expected to purchase some 75 million packets for worldwide distribution. UNICEF usually distributes directly to ministries of health for national or WHO-sponsored programs.

It is estimated that about 400 million children under the age of 5 live in developing countries, excluding China (Population Information Program 1984). Therefore, 2.4 billion packets of ORS would be required annually for the treatment of diarrheal diseases, assuming that each child requires about six packets a year. To fill this need, developing countries are being

encouraged to implement national or regional production of ORS packets. UNICEF and A.I.D. are providing technical assistance in the purchase of equipment, raw materials, and supplies (United Nations Department of International Economic and Social Affairs 1978). National production is likely to be more costly initially than is international procurement of ORS packets. The most economical approach for some developing countries choosing to produce their own packets is to purchase premixed ORS in bulk from UNICEF and to subdivide the bulk shipments into packets.

3. PROJECT ADMINISTRATION

This project was undertaken initially under the direction of Dr. Rosalyn Cain King, principal investigator and director of International Health Institute of the Charles R. Drew University of Medicine and Science and Dr. Ira C. Robinson, co-principal investigator. However, in September 1986, Dr. Robinson severed his relationship with Drew. Drew promptly replaced Dr. Robinson with Dr. Bhaskar Chaudhuri, who has extensive experience in tablet formulation and is on the faculty of Xavier University, also a historically black university (HBCU).

The plan of work for the project at Xavier consisted of three phases:

1. Preparation of work plan, recruitment of required personnel, acquisition of certain apparatus, and installation of equipment.
2. Formulation of granules and tablets and evaluation of tablet forms under varying temperatures.
3. Physical and chemical analyses to permit stability comparisons, comparisons of the physical and chemical stability of formulations and tablets, and preparation and submission of a final project report.

The Xavier plan of work did omit research on the use of varying containers as was originally proposed. Unanticipated problems and constraints delayed the timely implementation of various aspects of the project, and therefore a no-cost extension was requested and granted so that all phases could be completed.

The project objectives, methodology, results, and implications are summarized in the following sections.

disintegration and solution.)

Each formulation was tested for the following at start-up and at specified time intervals (2, 5, and 10 days) in accordance with the stability testing protocol.

1. Weight variation in accordance with procedures of USP XXI for tablets that are not taken orally. ORS tablets are dissolved and the prepared solution is then taken by mouth.
2. Moisture content, using official USP XXI procedures.
3. Friability--A Roche friabilitor was used. A test sample of 10 tablets was placed in the tumbling drum of the friabilator, which was rotated at 25 rpm for 15 minutes. The percentage loss in weight for the tablets was determined by brushing the remaining intact tablets with a camel hair brush to remove any adhering powder, weighing the brushed intact tablets, calculating the loss in weight, and dividing the loss in weight by the initial weight of the test sample. Triplicate tests were run, and the average friability (percentage weight loss) was determined.
4. Dissolvability--Triplicate samples of each tablet test formulation equivalent to the corresponding amount of ORS powder for the preparation of 200-mL of ORS solution were added to 200-mL of distilled water in a 250-mL flask, shaken for 5 minutes on a mechanical shaker, and evaluated for completeness and clarity of solution. If

a test sample did not dissolve completely within 5 minutes, it was shaken again for an additional 5 minutes and observed.

The experimental design was established as detailed here; the study was undertaken as established with any exceptions noted in section 5, Research Methods and Procedures.

5. RESEARCH METHODS AND PROCEDURES

The procedures and experimental design detailed in section 4, Experimental Design, were followed unless otherwise noted in this section, which summarizes these procedures by task.

5.1 Experimental Materials

To experiment with various tablet formulations, the following chemicals and substances were used: sodium chloride, sodium acetate, sodium citrate, potassium chloride, glycine, cornstarch, ammonium thiocyanate, crystal violet, methyl orange, perchloric acid, nitrobenzene, and magnesium stearate; ferric ammonium sulfate, dextrose, and talc; glacial acetic acid, nitric acid, and sulfuric acid; silver nitrate; and ricestarch.

5.2 Methods

The methods and procedures employed in this study are detailed in section 4, Experimental Design. Deviations will be noted in this section, but the full procedure will not be repeated.

5.2.1 Preparation of Binders

Cornstarch was used in preparing the pastes to be used as binders. These pastes were prepared in the conventional fashion. A 10-percent starch paste was used in all cases. The requisite amount of dry cornstarch powder was dispersed in cold water and then heated at a temperature of 80 ± 1 deg C with constant stirring. The paste thus formed was cooled to room temperature.

5.2.2 Preparation of Granules

The procedures detailed in section 4.1 were followed to prepare granules.

The recommended WHO formulations were used for preliminary studies. Specific quantities of the 10-percent starch paste (8, 12, and 16-g) were added to the formulations to find the optimum quantity required. The amount was considered to be optimum if the powder mass formed a "dough" that crumbled into large pieces with slight pressure of the hand. The optimum amount was determined to be 12-g for a batch size of approximately 55-g. All the batches of granules were prepared using this proportion, or multiples thereof, unless otherwise mentioned.

The conventional wet granulation technique was used to prepare the granules. The ingredients of each of the formulations were mixed thoroughly, and the starch paste was added to the mixture. Mixing was performed slowly by hand and a dough-like consistency was obtained. The wet mass thus prepared was passed through an 8-mesh screen to yield the wet granules.

The next step consisted of drying the granules. The mass was spread evenly on small trays and kept in an air-oven maintained at 40 deg C until the granules were dried to a moisture content of 1 percent as required for tabletting. The moisture content was determined by using a moisture balance. However, it was noticed that, at the end of the drying period, the granules attained a brown color indicating the possibility of charring or degradation of some of the ingredients. To prevent charring of the granules,

a totally different drying approach was tried. Granules were dried using a fluid bed dryer that was maintained at 45 deg C. This decreased the drying time to a marked extent. As was mentioned earlier, the granules were dried to a moisture content of 1 percent. The dried granules were forced through a 12-mesh screen for tabletting.

5.2.3 Testing Procedures for Granules

The tests performed on the dried unlubricated granules included the following (all values, where applicable, were repeated in triplicate.):

Bulk density. The bulk densities of the granules were determined by weighing out 50-g batches and placing them in a 100-mL graduated cylinder. The cylinder was dropped onto a wooden surface three times (Parrott and Saski 1977). Care was taken to see that the intensity of each "tap" was the same by allowing the cylinder to fall from a height of approximately 2-cm. The volume and the weight were recorded to calculate the apparent density of the granule preparation.

Granule density. Granule densities of the various preparations were determined by using a specific gravity bottle with toluene as the supernatant liquid (Khan and Rhodes 1975).

Porosity. The interspace porosity, or void porosity, is the relative volume of interspace voids to the bulk volume of the powder, exclusive of intrapartical pores. The interspace porosity was computed from a knowledge of the bulk density and the granule density, already mentioned, and is expressed by the following

equation.

$$\text{porosity (interspace)} = 1 - \frac{\text{bulk density}}{\text{granule density}}$$

The final value is expressed as a percentage.

Flow rate. The flow rate for all the granule preparations was found by allowing 50-g of the mass to pass through a standard funnel and measuring the time, as was described by Jalal, Malinowski, and Smith (1972).

Friability. The friability data for the granules were found by using a modification of the method of Hill (1976). The granules were weighed (25-g) and placed in a Roche Friabilator for a period of 5 minutes. The powder finer than 60-mesh, generated by tumbling, was sifted off after the stipulated period and weighed to get the friability. The result is expressed as a percentage.

Sieve analysis. The best idea about granule size distribution can be obtained by sieve analysis. This was performed by using a sieve shaker with seven settings. The shaker with mesh numbers of 14, 18, 20, 40, 60, and 80 and the pan was operated for 5 minutes with a 200-g sample size. The amount remaining on each mesh was weighed and reported as a percentage.

5.2.4 Preparation of Tablets

The procedures detailed in section 4.2 were followed to prepare tablets.

Before compression, the dry granules were lubricated with 0.5-percent magnesium stearate. A 1-percent concentration of talc was also added to serve the dual purpose of an antiadherent and glidant. To expedite disintegration, cornstarch powder (1 percent) was added as the disintegrant. The granule preparation was placed in the hopper of the single-punch tablet machine to form the tablets. For final preparation of the tablets, the Carver press was used. Tablets were made with a diameter of 1 inch and a weight of 5-g at a pressure of 8,000 psi to give the required hardness.

5.2.5 Testing Procedures for Tablets

The evaluation of the physical properties of the tablets were performed through the following tests.

Weight and standard deviation. Ten tablets from each batch were dusted and individually weighed to the nearest 0.1 mg. The average tablet weights and standard deviation were calculated.

Coefficient of variation. The coefficient of variation values were calculated from the weight and standard deviation data and reported as percentages.

Porosity. The porosity of the tablets was found by the same procedure as that described for the granules except that the tablet density was taken to be the bulk density. The tablet density was calculated from the available values of thickness, diameter, and weight.

Thickness. Tablet thickness measurements were made to the nearest 0.01 mm. The reported thickness value was the average

thickness of the 10 tablets.

Dissolution time. A U.S. pharmacopeial dissolution instrument was used to test the rapidity with which the tablets dissolved. Method 2 of the USP XXI (p. 1244) was used. The tablet was dropped into the dissolution vessel containing water (1,000-mL), and the paddle was used to stir the solution at the rate of 100 rpm. The time taken for the tablet to dissolve completely was recorded as the dissolution time.

Friability. The friability of the tablets was determined in the same way as that for the granules. Each of the tablets were placed in the Roche Friabilator and rotated for 5 minutes. The powder generated was sifted off in a 60-mesh screen, and the tablets were weighed to record the loss. The values are reported as percentages.

5.2.6 Chemical Analysis

The chemical analysis in all cases was performed in accordance with USP XXI and stipulated by the protocol. Assays were attempted for sodium chloride and potassium chloride because they existed in all formulations in the same proportion. Quantitation was also performed for glycine where applicable.

Sodium chloride A weighed portion (4-g) of the crushed tablets was dissolved in approximately 100-mL of water and filtered into a 500-mL volumetric flask. The filter and original container were then washed with 100-mL of water in divided portions, and these portions were then added to the original filtrate. The filtrate was then diluted with water to volume. A

volume of the solution equivalent to 250-mg of sodium chloride was then pipetted into a glass-stoppered flask and diluted with water to 50-mL. To this sample was added 50-mL of 0.1N silver nitrate, 3-mL of nitric acid, 5-mL of nitrobenzene,and 2-mL of ferric ammonium sulfate. The sample was then shaken well, and the silver nitrate was titrated with 0.1N ammonium thiocyanate. Each milliliter of 0.1N silver nitrate is equivalent to 5.844-mg of sodium chloride.

Potassium chloride. A 250-mg sample of the crushed tablet was dissolved in 50-mL of water and placed in a glass-stoppered flask. To this sample was added 50-mL of 0.1N silver nitrate, 3-mL of nitric acid, and 5-mL of nitrobenzene; there was constant agitation. The sample was then shaken vigorously, and the excess silver nitrate was titrated with 0.1N ammonium thiocyanate. Each milliliter of 0.1N silver nitrate is equivalent to 7.455-mg of potassium chloride.

Glycine. To a 250-mL flask, 150-mg of the crushed tablet was transferred and dissolved in 100-mL of glacial acetic acid. To this solution was added one drop of crystal violet TS. The solution was then titrated with 0.1N perchloric acid to a green end-point. Blank determinations were performed, with necessary corrections being made. Each milliliter of 0.1N perchloric acid is equivalent to 7.507-mg of glycine.

5.2.7 Stability Testing

The following stability tests were performed.

Effect of temperature. Tablets from each batch were

subjected to elevated temperatures to record changes. Convection ovens were maintained at constant temperatures of 50 and 70 deg C, and tablets (one at each temperature) were kept in the ovens for 10 days. A third set of tablets was kept at room temperature (25 deg C). Samples of tablets were withdrawn at the end of 2, 5, and 10 days to perform the various tests.

Effect of humidity. Humidity chambers were used to study the effect of moisture on the tablets. Various combinations of the wet bulb temperature and dry bulb temperature were used to obtain the desired humidities. The combinations of the temperatures used were obtained from the CRC Handbook of Chemistry and Physics (1986). The humidity chambers were set at 25 deg C and relative humidities of 70 and 90 percent.

6. STUDY RESULTS AND DISCUSSION

The choice of the method of tablet preparation is quite important. Direct compression is probably the best available method for preparing tablet alternatives for ORS. It is simple and fast and does not require modification of the physical nature of the material. In addition, the absence of binders would mean even faster tablet dissolution and increased patient compliance. The entire process is less tedious than others and thus is becoming widely used. For these reasons, the investigators decided to prepare the tablets by direct compression.

The total weight of the WHO ORS formulation, for 1 liter of water, is 27.5-g for the original formula (bicarbonate) and 27.9-g for the new formula (citrate). If these formulations are to be made for home use, the amount should be decreased such that no storage of the water is required. An optimum formulation is one that can be taken as a single dose in one glass of water (approximately 240-mL). If the ORS formulation can be dissolved in a glass of water, patient compliance will increase. The amount of ORS preparation to be dissolved should be one-forth of the original formula weight, approximately 6.9-g per dose. With this in mind, preparation of tablets weighing 3.5-g will be ideal, as two of these dissolved in a glass of water give the desired nourishment.

The single-punch tablet press and the Carver Press were used to form the tablets. Punches were ⅜ and ½-inch for the single-punch machine and 1 inch for the Carver Press. A weight of

3.5-g was too heavy for a ½-inch punch on a single-punch machine and too small for a 1-inch punch on a Carver Press. Thus the single-punch machine was used to set the characteristics of the tablet formulation, and the Carver Press was used to make the final tablets. Five grams was determined to be the optimum weight for the Carver Press. The primary goal of this study was to investigate the feasibility of having an ORS tablet formulation. If the physical and chemical attributes of the formulation are suitable, changing the size of the tablet, if necessary, will be a minor problem.

To determine the variables associated with the preparation of the ORS tablet, preliminary studies were undertaken with the WHO formulations. They were weighed as follows:

ORS bicarbonate

	GRAMS
Sodium chloride	7.0
Sodium bicarbonate	5.0
Potassium chloride	3.0
Anhydrous glucose	40.0

ORS citrate

	GRAMS
Sodium chloride	7.0
Sodium citrate	5.8
Potassium chloride	3.0
Anhydrous glucose	40.0

The above combinations were mixed thoroughly and fed into the hopper of the single-punch press with the machine adjusted to give

tablets weighing 600-mg and having thicknesses of 0.4-cm. The flow property of both formulations were uneven, resulting in tablets with weight variations in most cases in excess of 15 percent. A 1-percent concentration of talc was added to the mass as a lubricant. This decreased problems with tablet uniformity, however, the tablets were "soft." Even when the pressure in the machine was increased, the hardness of the tablets decreased and the particles lacked the ability to stick or bind together. Increasing pressure above 10-kg caused the punches to stick. This problem was more severe in the case of the ORS citrate formulation. As a result of this preliminary study, the investigators decided that a binder would be appropiate because it would give the desired hardness and reduce the friability.

The first step then was the choice of binders. At present there are may binders available. However, because these formulations will be used primarily in developing countries, starch paste was chosen because of its proven ability and abundance throughout the world.

Various combinations of salts and additives were used in the formulations as outlined in this report. The basic method used in preparing the granules and finally the tablets was the same for all cases for comparison purposes. The combination of ingredients used in the different formulations are outlined in Tables 1 through 3. It should be noted that the amount of cornstarch paste (used as the binder) in most cases was the same except when more of the paste was needed to form the "doughy" mass. The physical

properties of the granules prepared by the wet granulation technique are listed in Table 4. The sieve analysis data are shown in Table 5. The presence of glucose caused the bulk density to decrease. The absence of glucose, starch, or glycine, on the other hand, caused the bulk densities to increase as was evidenced in groups 1A and 3A. No other trends were obvious for the other properties. Changes in the amount of binder would probably have caused the properties to differ noticeably.

The sieve analysis data give insight into the granule sizes of the groups and an idea of distribution. These studies were performed with the hope of correlating them with friability values. Granule friability decreases, in general, in groups containing larger granules.

The ultimate evaluation of tablet granulation lies in the tabletting characteristics. To eliminate variables, the compression pressure was kept constant for all batches. Thus, the tablets became completely dependent on the individual properties of the granulations from which they were compressed. The physical properties of the tablets for different batches are shown in Tables 6 through 8. Neither tablet weights, their standard deviations,

TABLE 1- FORMULATIONS CONTAINING SODIUM ACETATE

INGREDIENTS	Groups (Amounts in grams)				
	1	1A	1B	1C	1D
Sodium Chloride	100.5	100.5	100.5	100.5	100.5
Potassium Chloride	45.0	45.0	45.0	45.0	45.0
Sodium Acetate	81.0	81.0	81.0	81.0	81.0
Glucose	600.0				
Glycine			167.5	167.5	167.5
Corn Starch Powder				40.0	
Rice Starch Powder					40.0
Starch Paste	60.0	60.0	60.0	60.0	60.0

Blank spaces indicate that the ingredient was not included in the formulation.

TABLE 2- FORMULATIONS CONTAINING SODIUM BICARBONATE

INGREDIENTS	Groups (Amounts in grams)				
	2	2A	2B	2C	2D
Sodium Chloride	100.5	100.5	100.5	100.5	100.5
Potassium Chloride	45.0	45.0	45.0	45.0	45.0
Sodium Bicarbonate	75.0	75.0	75.0	75.0	75.0
Glucose	600.0				
Glycine			167.5	167.5	167.5
Corn Starch Powder				40.0	
Rice Starch Powder					40.0
Corn Starch Paste	120.0	60.0	60.0	60.0	60.0

Blank spaces indicate that the ingredient was not included in the formulation.

TABLE 3- FORMULATIONS CONTAINING SODIUM CITRATE

INGREDIENTS	Groups (Amounts in grams)				
	3	3A	3B	3C	3D
Sodium Chloride	100.5	100.5	100.5	100.5	100.5
Potassium Chloride	45.0	45.0	45.0	45.0	45.0
Sodium Citrate	87.0	87.0	87.0	87.0	87.0
Glucose	600.0				
Glycine			167.5	167.5	167.5
Corn Starch Powder				40.0	
Rice Starch Powder					40.0
Corn Starch Paste	60.0	60.0	60.0	60.0	60.0

Blank spaces indicate that the ingredient was not included in the formulation.

Table 4-PHYSICAL PROPERTIES OF GRANULES

GROUPS	Bulk density (g/ml)	Granule density (g/ml)	Porosity (%)	Flow rate (g/sec)	Friability (%)
1	0.53	1.4712	63.85	8.33	1.04
1A	0.76	1.7156	55.16	13.33	1.46
1B	0.74	1.4485	48.48	10.00	5.46
1C	0.64	2.1260	69.46	10.00	9.82
1D	0.64	1.6029	54.60	14.20	0.22
2	0.58	1.5161	61.65	12.50	1.00
2A	0.67	1.9730	65.76	12.50	1.20
2B	0.70	1.6960	58.03	11.40	0.82
2C	0.65	1.5150	34.00	14.00	0.68
2D	0.71	1.6164	50.58	16.60	2.07
3	0.52	1.5646	66.36	12.50	0.35
3A	0.78	1.8900	58.66	16.66	1.03
3B	0.68	1.7300	60.49	13.71	1.01
3C	0.55	0.9850	43.61	10.00	0.41
3D	0.71	1.6367	39.75	12.50	0.68

Table 5-SIEVE ANALYSIS DATA OF GRANULE

GROUPS	% remaining on mesh number						
	14	18	20	40	60	80	Pan
1	75.68	8.57	10.05	5.19	0.51	0.00	0.00
1A	28.76	15.26	25.69	26.30	3.30	0.46	0.23
1B	26.51	13.57	21.68	27.29	7.45	1.73	1.77
1C	25.43	11.93	18.55	29.20	10.23	2.33	2.33
1D	45.40	27.80	46.80	61.20	9.20	1.70	1.20
2	13.33	12.58	26.85	40.31	6.57	0.33	0.03
2A	24.10	15.30	22.51	27.42	7.22	2.45	1.01
2B	22.37	16.97	25.27	25.34	6.47	1.75	1.83
2C	42.07	12.40	17.90	17.27	5.49	2.36	2.51
2D	36.10	24.00	39.20	59.70	14.30	4.00	0.00
3	24.06	17.38	27.81	25.13	5.21	0.27	0.13
3A	30.90	25.30	39.60	44.10	10.50	2.40	4.00
3B	19.23	11.36	20.47	30.37	9.91	3.20	5.46
3C	27.13	14.13	22.00	28.36	5.82	1.14	1.62
3D	61.50	22.80	48.90	48.30	7.40	0.50	0.00

Table 6- PHYSICAL PROPERTIES OF TABLETS CONTAINING SODIUM ACETATE

Groups	Weight (±S.D.) (g)	Coefficient of variation (%)	Porosity (%)	Thickness (mm)	Dissolution time (min.)	Friability (%)
1	4.9820 (0.0528)	1.5	23.37	5.17	11	1.6
1A	5.0047 (0.0431)	0.86	12.47	5.03	21	1.9
1B	5.0241 (0.0625)	1.2	27.58	4.97	45	1.2
1C	5.0481 (0.0558)	1.1	8.46	4.93	28	1.05
1D	5.0579 (0.0716)	1.4	15.29	5.16	65	3.05

For each weight, the standard deviation is given parenthetically.

Table 7- PHYSICAL PROPERTIES OF TABLETS CONTAINING SODIUM BICARBONATE

Groups	Weight (±S.D.) (g)	Coefficient of variation (%)	Porosity (%)	Thickness (mm)	Dissolution time (min.)	Friability (%)
2	4.9185 (0.0378)	0.76	18.06	5.27	37	0.29
2A	4.9605 (0.0604)	1.2	13.09	4.35	32	0.45
2B	4.9373 (0.0399)	0.5	13.03	5.03	27	3.60
2C	5.0047 (0.0438)	0.8	18.11	5.26	5	0.20
2D	4.9838 (0.0379)	0.76	17.13	5.11	2	0.89

For each weight, the standard deviation is given parenthetically.

Table 8- PHYSICAL PROPERTIES OF TABLETS CONTAINING SODIUM CITRATE

Groups	Weight (±S.D.) (g)	Coefficient of variation (%)	Porosity (%)	Thickness (mm)	Dissolution time (min.)	Friability (%)
3	5.0333 (0.0464)	0.92	12.63	5.54	20	0.58
3A	5.0188 (0.0350)	0.69	9.57	4.77	17	0.96
3B	4.9946 (0.0711)	1.42	35.45	5.22	19	6.80
3C	5.0066 (0.0393)	0.78	38.37	6.17	5	1.99
3D	4.9945 (0.0541)	1.00	15.24	5.12	65	1.90

For each weight, the standard deviation is given parenthetically.

nor the coefficient of variation showed any definite correlation. The porosity values indicated that the tablets containing sodium bicarbonate had high porosity values, and the dissolution times for these were longer. The friabilities were quite low except those for group 3B. The dissolution time was highest for group 3D. No obvious correlation was seen between the different parameters.

As was mentions in section 5.2, Methods, the chemical analyses were performed in accordance with the USP XXI procedures as stipulated by the protocol. The USP XXI procedures are specified for tablets containing only one main ingredient (sodium chloride, potassium chloride, etc.). This placed a serious constraint on the analysis of the ORS formulations because each contains more than one salt. Assays were specific for one ingredient, thus quantitation became a problem because of interference (e.g., sodium chloride interfered with potassium chloride as the chloride was being quantitated). Each of the tests gave values higher than the theoretical values. As a result, interferences from chemical analysis could not be drawn.

Stability of the tablets was studied varying the humidity and the temperature. Although the tablets were kept in glass jars, they started melting at 50-percent relative humidity. None of the physical parameters could be effectively studied because the individual tablets became sticky or soggy. Some of the tablets eroded partially due to the high moisture content. Results with 70-percent relative humidity were more drastic. Of course, these observations were expected because of the percentage of highly

water-soluble ingredients.

Dissolution time, friability, and visual changes were observed to measure the effect of temperature on the physical properties of the tablets and thereby give the indication of its stability. Dissolution time changes on start-up (day 0) and at the end of 2, 5, and 10 days are shown in Tables 9 through 11. The general trend observed for the dissolution times was that it decreased with time if stored at room temperature (25 deg C). Absorbed moisture at room temperature may have facilitated dissolution. The observation was reversed at 50 and 60 deg C. However, in most cases, the dissolution time did not change drastically after day 2. In nearly all cases, the dissolution medium remained turbid. This observation was more predominant in cases where starch was present (rice starch being the most turbid).

The friabilities of the various preparations are shown in Tables 12 through 14. No significant trend was observed for any of the groups. The visual appearance tabulated on Tables 15 through 17, however, indicate marked changes. The tablets changed color, appeared mottled, and developed fissures and cracks. Some of them became soggy, and others turned powdery.

TABLE 9- COMPARISON OF DISSOLUTION TIMES AT ROOM TEMPERATURE

Groups	Dissolution time (in minutes)*			
	Day 0	Day 2	Day 5	Day 10
1	11	11	9	8
1A	21	21	20.5	20
1B	45	44	35	33
1C	28	27	26	22
1D	65	30	1	1
2	37	36	35	33
2A	32	24	11	9
2B	27	25	25	22
2C	5	4	4.5	4
2D	2	2	1.5	0.5
3	20	17	2	0.5
3A	17	16	16	16
3B	19	18	18	20
3C	5	4	2.5	5
3D	65	29	1	1

* Mean of three readings.

TABLE 10-COMPARISON OF DISSOLUTION TIMES AT 50° C

Groups	Dissolution time (in minutes)*			
	Day 0	Day 2	Day 5	Day 10
1	11	22	10	16
1A	21	50	48	46
1B	45	30	26	24
1C	28	40	38-39	35
1D	65	2.5	2	1.5
2	37	38	34	26
2A	32	N/A°	N/A°	N/A°
2B	27	28	24	20
2C	5	10	4-5	4
2D	2	1	0.5	0.5
3	20	45	43	44-45
3A	17	8.5	8.5	8.5
3B	19	9	8	8
3C	5	3.5	3.5	3
3D	65	1	0.5	0.5

* Mean of three readings.
° Did not dissolve at the end of ninety minutes

TABLE 11-COMPARISON OF DISSOLUTION TIMES AT 60 ° C

Groups	Dissolution times (in minutes)*			
	Day 0	Day 2	Day 5	Day 10
1	11	22	18	20
1A	21	45	46	42
1B	45	30	23	22
1C	28	38	37	33
1D	65	11	0.5	0.5
2	37	35	30	28
2A	32	N/A°	N/A°	N/A°
2B	27	25	20	18
2C	5	18	3.5-4	3.5-4
2D	2	2	1	0.5
3	20	40	32	34.5
3A	17	7.5	7.5	34
3B	19	9	8.5	8
3C	5	3	2.5	2.5
3D	65	0.5	0.5	0.5

* Mean of three readings.
° Did not dissolve at the end of ninety minutes

TABLE 12-COMPARISON OF FRIABILITY AT ROOM TEMPERATURE

Groups	Friability time (in minutes)*			
	Day 0	Day 2	Day 5	Day 10
1	1.6	0.21	0.24	(a)
1A	1.9	1.9	0.55	0.19
1B	1.2	0.12	0.60	(a)
1C	1.05	0.1	0.21	(a)
1D	3.05	1.9	1.06	(a)
2	0.29	0.02	0.19	0.13
2A	0.45	0.12	0.01	0.05
2B	3.6	2.56	3.0	1.48
2C	0.2	1.36	0.8	1.30
2D	0.89	1.34	0.83	(a)
3	0.58	0.67	0.75	0.37
3A	0.96	3.29	4.02	0.75
3B	6.80	4.00	2.43	.84
3C	2.99	0.05	0.46	0.48
3D	1.90	4.80	5.30	(a)

Mean of three trails.
(a) Tablet turned soggy.

TABLE 13-COMPARISON OF FRIABILITY AT 50° C

Groups	Friability time (in minutes)*			
	Day 0	Day 2	Day 5	Day 10
1	1.6	0.31	0.14	0.23
1A	1.9	0.46	1.90	0.33
1B	1.2	0.04	0.08	0.23
1C	1.05	0.25	0.13	0.2
1D	3.05	0.86	0.62	0.9
2	0.29	0.05	0.07	0.11
2A	0.45	1.25	2.26	0.78
2B	3.6	1.67	3.25	2.7
2C	0.2	1.47	1.63	1.5
2D	0.89	2.10	5.14	3.2
3	0.58	0.03	0.29	0.17
3A	0.96	4.9	4.48	6.4
3B	6.80	2.7	4.21	4.5
3C	2.99	0.04	1.37	1.7
3D	1.90	4.2	6.16	4.6

Mean of three trails.

TABLE 14-COMPARISON OF FRIABILITY AT 60° C

Groups	Friability time (in minutes)*			
	Day 0	Day 2	Day 5	Day 10
1	1.6	0.03	0.04	0.91
1A	1.9	1.5	1.48	2.27
1B	1.2	0.23	0.10	0.12
1C	1.05	0.01	0.37	0.23
1D	3.05	0.48	2.16	0.80
2	0.29	0.09	0.21	0.04
2A	0.45	1.10	1.90	1.20
2B	3.6	2.9	2.5	4.04
2C	0.2	2.19	0.8	3.9
2D	0.89	2.9	0.18	1.45
3	0.58	0.22	0.76	0.78
3A	0.96	6.0	4.8	6.74
3B	6.80	3.9	4.34	10.71
3C	2.99	1.3	5.36	0.63
3D	1.90	2.6	3.6	0.96

* Mean of three trails.

TABLE 15-COMPARISON OF VISUAL OBSERVATIONS OF TABLETS AT ROOM TEMPERATURE

Groups	Visual Observations			
	Day 0	Day 2	Day 5	Day 10
1	D.W.	D.W.	D.W. (moist)	D.W. (moist)
1A	C.W.	C.W.	C.W.	C.W. (fissures)
1B	C.W.	C.W. (moist)	C.W. (moist)	C.W. (moist tablet partially dissolved)
1C	C.W.	C.W. (moist)	C.W. (moist)	C.W. (moist tablet partially dissolved)
1D	D.W.	D.W. (fissures)	D.W. (fissures)	D.W. (moist)
2	D.W. (mottled)	D.W. (increased mottling)	increased mottling	yellowish brown
2A	C.W.	C.W.	C.W.	C.W. (moist)
2B	C.W.	C.W.	C.W. (moist)	C.W. (moist)
2C	C.W.	C.W.	moist yellowish brown	yellowish brown partially dissolved
2D	D.W.	D.W.	D.W.	D.W. (powdery)
3	C.W.	C.W.	C.W.	C.W.
3A	C.W.	C.W.	C.W.	C.W.
3B	C.W.	C.W.	C.W.	C.W.
3C	C.W.	C.W.	C.W.	C.W.
3D	D.W.	D.W.	D.W.	D.W. (moist)

C.W.= Crystal White
D.W.= Dull White

TABLE 16-COMPARISON OF VISUAL OBSERVATIONS OF AT TABLETS 50° C

Groups	Visual Observations		
	Day 2	Day 5	Day 10
1	yellowish brown moist	yellowish brown moist	amber, moist
1A	C.W.	C.W. (brownish center)	increase mottling
1B	C.W.	C.W.	C.W.
1C	D.W.	D.W.	D.W.
1D	D.W.	D.W.	D.W.
2	brown	brown	brown
2A	C.W.	C.W.	C.W.
2B	C.W.	C.W. (irregular mottling)	D.W.
2C	C.W.	D.W.	D.W
2D	D.W.	D.W.	D.W. (powdery)
3	C.W.	C.W.	C.W.
3A	C.W.	C.W.	C.W. (powdery)
3B	C.W.	C.W. (powdery)	C.W. (powdery)
3C	D.W.	D.W.	D.W.
3D	D.W.	D.W.	D.W.

C.W.= Crystal White
D.W.= Dull White
On day 0, all groups were crystal white.

TABLE 17-COMPARISON OF VISUAL OBSERVATIONS OF TABLETS AT 60° C

Groups	Visual Observations		
	Day 2	Day 5	Day 10
1	orange-brown moist	orange-brown moist	deep-brown moist
1A	C.W.	C.W.	C.W.
1B	C.W.	C.W.	yellowish-brown
1C	C.W.	C.W.	D.W.
1D	D.W.	D.W.	D.W. (fissures)
2	yellowish brown	brown	brown
2A	C.W.	C.W.	C.W.
2B	C.W.	C.W.	D.W.
2C	C.W.	C.W.	D.W (mottled)
2D	D.W.	D.W.	D.W.
3	D.W.	D.W.	D.W. (mottled)
3A	C.W.	C.W.	C.W
3B	D.W. (mottled)	D.W. (mottled)	D.W. (mottled fissure)
3C	C.W.	C.W.	D.W.
3D	D.W.	D.W.	D.W.

C.W.= Crystal White
D.W.= Dull White
On day 0, all groups were crystal white.

7. STUDY CONCLUSIONS AND IMPLICATIONS

A general overview of the tablet formulations and their physical properties shows that no single group emerges as an outstanding candidate for tablet formulation. On the other hand, none of them could be ruled unsuitable. This study indicates that although there are some serious problems, the WHO ORS formulation can be made into a tablet dosage formulation. It should be noted that patient compliance is of prime importance if these tables are for home use. Therefore, dissolution speed and clarity of the resulting solution are of prime importance. The tablets prepared in this study lack both these requisites. Although starch paste is an effective binder, clarity becomes a problem. Other synthetic binders (different grades of PVP) could be tried. The concept of cereal-based ORS tablet formulations becomes questionable when clarity is a factor. Dissolution should be fast, if not instantaneous, for patient compliance. This can probably be achieved with the incorporation of agents such as modified cellulose gum that accelerate dissolution.

Finally, the effect of humidity on such preparations should be noted. This relates directly to the storage containers and conditions used, and thus the effectiveness of various packaging materials should be tested. The formulation, whatever its form, will be water soluble and will have the tendency to absorb moisture to some extent. Thus, complete protection form moisture is essential. Formulation of a tablet alternative for home ORT is promising; however, more long-term experiments must be conducted before conclusive statements can be made.

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