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Formulation Studies of Tableted Oral Rehydration Salt Mixtures

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Abstract—Dehydration following non-specific diarrhoea may be prevented by oral administration of a simple glucose/salt mixture. A solution tablet of this mixture would have advantages of stability under environmental exposure and transport if the costs could be held within reasonable limits. The moisture adsorption and compression characteristics of Oral Rehydration Salts (ORS) ingredients have been studied. Combinations of ingredients resulted in a moisture adsorption higher than that of the individual components. This may be explained in terms of critical relative humidity, RHo, and environmental relative humidity RHi. Preparation of a stable ORS solution tablet therefore requires protection of moisture adsorbing components from the environment. The present UNICEF ORS mixture compacted easily by direct compression but gave fragile tablets, which were hygroscopic. This can be reduced by film coating the electrolyte component as granules with a resin (Eudragit L), or by simulating direct compression of the glucose as a compression-coating around the precompressed electrolytes. The packaging of compression-coated solution tablets in inexpensive polyethylene bags may lengthen the shelf-life and make the preparation less costly than the currently supplied ORS powders packed in laminated aluminium sachets. The increased dissolution lag time for the compacted tablet is a disadvantage that can be overcome by instructions to crush the product immediately before use.

A major cause of infant death in developing countries is dehydration due to water loss and the associated depletion of essential minerals from non-specific diarrhoea (Swift & Hamilton 1973; Snyder & Merson 1982). Research in India and elsewhere (Hirschorn et al 1968; Nalin et al 1979; Finberg 1980) led to the development of an oral rehydration salt (ORS) mixture (Table 1) that is regarded as a major technical advance in the reduction of mortality due to this disease (Editorial 1978; Mauer et al 1985; WHO 1985).

To date, some 42 developing countries have undertaken the production of ORS (Merson 1987). UNICEF however, continues to be the largest external supplier of ORS packets for use in preparation of a one pint solution. This mixture is relatively unstable, becoming discoloured, especially when containing bicarbonate, and rapidly takes up water. This necessitates the use of foil-laminated plastic sachets. While the ingredients for a one litre solution may cost 25c (US), the packaging material costs a disproportionate 20c, smaller packets being even more expensive. These are additional costs that are not easily assimilated in developing countries (Population Reports 1980). The powder is also prone to separation of ingredients on transport and storage, as does any dry powder mix, it is difficult to sub-divide accurately, and the prepared solution is liable to show microbial growth on prolonged storage.

From a pharmaceutical perspective therefore, a solution tablet would be a more accurate dosage form and more flexible in terms of tailoring a solution for individual patients. In addition to being easier to package and transport, adequately packed solution tablets should be more stable than powders under the conditions of high humidity and temperature associated with tropical and subtropical conditions.

Izgu & Baykara (1981) investigated the solid state stability of ORS by examining the discolouration of the salts under different conditions. They found that the decomposition of glucose was markedly affected by sodium bicarbonate and was accelerated by temperature and humidity. The replacement of sodium bicarbonate by sodium citrate was shown to produce a more stable and equally effective preparation (Siewert & Gnekow 1983; Islam 1986). Unfortunately, under hot and humid conditions, this new preparation also absorbs moisture, discolours and cakes. Attempts to improve stability have been suggested but not evaluated (Patra et al 1982; Islam 1985). There is, therefore, a need to understand the moisture sorption characteristics of the ORS ingredients to improve stability. Understanding compressional behaviour is also desirable to prepare the often requested solution tablet form of ORS (Patra et al 1982; Islam 1985; D'Arcy 1987).

In the present study, the stability of the UNICEF ORS mixture and other suggested alternatives, both individually and in combination, was investigated by examining moisture sorption characteristics under controlled relative humidities. Compressional behaviour and the preparation of compressible and disintegrating glucose granules for use in ORS were also investigated. In addition, the formulation of a stable ORS tablet in which the hygroscopic character was reduced by coating the electrolyte components as granules with a resin (Eudragit L) or with the glucose component in a simulated compression coated tablet is reported.

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Materials and Methods

Materials

D(+)-Glucose, anhydrous[1]; citric acid, tripotassium salt[1]; sodium acetate, anhydrous[1]; ammonium dibasic phosphate monohydrate[1]; guar gum[2]; corn starch[2], potassium chloride USP[2], sodium citrate, dihydrate[2], potassium nitrate[2], sodium bicarbonate[3], ammonium chloride USP[3], ammonium sulphate[3], sodium carboxymethyl cellulose[3], sodium acetate, hydrous[4], barium chloride dihydrate[5] and Avicel[6] were all reagent grade unless otherwise stated. Directly compressible glucose was Emdex[7] a highly refined product of free flowing spray crystallized porous spheres of dextrins containing 93–99% dextrose equivalent (NFXVI). Eudragit L-100-55[8].

Equipment

Samples were sieved using USA standard testing sieves (ASTM E-11 specification) mounted on a vibratory 3 inch sieve shaker[9]. Samples were weighed on a Mettler AE 100 balance[10]. Slugs (5g) were compressed by a single punch Carver press[11] using an unlubricated 12·8 cm stainless steel punch and die set outfit No. 2090 at a rate of 18·65 cm min^{-1} to the limiting pressure noted in the text. These were crushed using an Erweka dry granulator type T9SZ[12].

Experiments were in triplicate. Tablets were tested for crushing strength using an Erweka[12] or Monsanto[13] tester. Granules were dried in a NAPCO model 620 convection oven[14].

Polyethylene minigrip bags[15], $25 \times 3 \times 004$, sealed with a Quik-Seal impulse Sealer model 210 were used for packaging studies. A National Incubator[16] kept at 30 ± 1°C was used for storage tests. A Vanderkamp 600 six-spindle dissolution tester[17], Fisher Recordall series 5000 recorder[18] and a YS1 model 32 conductance meter[19] with a 3403 Cell (K = 10/cm) were used for dissolution tests.

Moisture absorption of powders

The ingredients were sieved and particles with sizes between 75 and 180 μm retained. The powders (10 g total) were progressively mixed in a mortar and pestle and then further mixed by gently rolling in a glass jar for 5 min. From each preparation, a 0·5 g sample was accurately weighed in an aluminium moisture dish, 5 cm diameter, and dried to constant weight over phosphorus pentoxide. The samples were transferred to various constant relative humidity chambers (Weast et al 1986) using saturated aqueous solutions of ammonium chloride and potassium nitrate (68·6% RH), ammonium chloride (77·5% RH), ammonium sulphate (81·1% RH) and dibasic ammonium phosphate (92·9% RH). The samples were maintained at 30 ± 1°C. Gravimetric measurements were recorded at intervals for not less than 100 h or until the powder was in solution.

Direct compression of powder mixtures

Accurately weighed 0·5 g samples of each ingredient or the complete ORS formulation (A–E, Table 1) were compressed into tablets at various pressures ranging from 34 to 600 MPa using the Carver press as before, and a 1·25 mm stainless steel punch and die set. Tablets were compressed with an upward movement of 0·68 cm s^{-1} and held at the pre-set pressure for 30 s. Tablet crushing strength was measured within 30 min of preparation using an Erweka hardness tablet tester.

Preparation of granules

The electrolytes in the formulation (Formulations A–O, Table 1) were granulated individually and in combination using water in the ratio of 1 mL water: 10 g electrolyte powder. The wet mass (11 g) was passed through a stainless steel sieve (No. 10) and granules air dried at 55 ± 1°C for 2 h. Dry granules were prepared by breaking 5 g slugs which had been compressed at 170 MPa, using a dry granulator[12]. All granules were sieved and particles of 1·4–2·0 mm retained for use.

Compressible glucose granules were prepared by wet granulation as previously described. Dry granules were obtained by crushing 5 g slugs of Emdex which had been compressed at 35 MPa. In both cases, particles of sizes 300 μm to 1·0 mm were retained for use.

Film-coating

A solution of 6% w/v acrylic resin (Eudragit L) in absolute ethanol was used for coating granules. Spray coating was achieved using an apparatus described previously (Alkan et al 1988). The vibration and spraying conditions were controlled to give a film coat 5% w/w of the total dry granule weight.

Simulated compression coating of precompressed electrolytes

Granules of combined electrolytes (0·14 g) (Formulation A, Table 1) were compressed at 148 MPa in an unlubricated small concave die (r = 0·437 cm). Half the glucose (0·18 g) was introduced into a larger die (r = 0·64 cm). The compressed electrolyte core was introduced into the larger die and covered by the remainder of glucose (0·18 g). The preparation (0·5 g) was then compressed at 138 MPa.

Granulation of glucose for direct compression

To improve the compression characteristics of glucose, making up about 70% of ORS mixtures, a method was devised to give compressible and rapidly disintegrating glucose granules. To every 100 g of dry glucose powder, 40 mL of 40% glucose syrup was added slowly with continuous mixing. The wet mass was passed through a No. 10 sieve, the wet granules spread thinly and evenly on a flat tray and dried in an oven at 55 ± 1°C. At timed intervals, granule samples were removed and 0·5 g tablets compressed at known pressures. Tablet crushing strength was measured using a Monsanto tester. Tablet disintegration was assessed by measuring the time taken for a tablet to break apart leaving

1. Sigma Chemical Co., St Louis MO 63178. 2. J. T. Baker Chemicals Company, Phillipsburg, NJ. 3. Fisher Scientific Co. Fair Laura, NJ. 4. Merck and Co., Inc., Rahway, NJ. 5. Mallinkrodt Chemical Works, St Louis, MO. 6. FMC Corporation, Food and Pharmaceutical Products Division, Philadelphia. 7. Kindly supplied by Edward Mendell Company Inc. NY. 8. Rohm Pharma GMBH Westerstadt. 9. Gilson Company Inc., Worthington, Ohio. 10. Mettler Instrument Corporation, Hightstown, NJ. 11. Carver press model 2702. Fred S. Carver Inc. Milwaukee. 12. Erweka-Apparatebau Type TBT/S, Frankfurt and Main, W. Germany. 13. Monsanto Chemicals, St Louis, MO. 14. National Apparatus Company, Portland, Oregon. 15. J and J Packaging, Elmhurst, Ill., 16. National Instrument Company Inc. Taiwan. 17. Van-Kel Industries, Inc. Edison, NJ. 18. Huston Instruments, Austin, Texas. 19. Yellow Spring Instrument Co., Inc. Yellow Springs, Ohio.

Table 1. Formulations investigated (g ingredients L^{-1} water).

Ingredient	Formulation* A**	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Glucose	20·0	20·0	20·0	20·0	20·0	20.0	20.0	20.0	—	—	—	20·0	20·0	20·0	—
Sodium chloride	3·5	3·5	2·3	2·3	2·3	3·5	—	—	3·5	3·5	—	3·5	—	3·5	3·5
Potassium chloride	1·5	—	1·5	1·5	1·5	—	1·5	—	1·5	—	1·5	1·5	1·5	—	1·5
Sodium citrate	2·9	—	—	1·5	—	—	—	2·9	—	2·9	2·9	—	2·9	2·9	2·9
Sodium bicarbonate	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Potassium citrate	—	6·5	—	—	—	—	—	—	—	—	—	—	—	—	—
Sodium acetate	—	4·1	2·1	—	—	—	—	—	—	—	—	—	—	—	—
Sodium acetate anhyd	—	—	—	—	2·5	—	—	—	—	—	—	—	—	—	—

* The ratios used were the same as in the UNICEF formula or were calculated to give this same molar concentration of the electrolytes.
** Current UNICEF ORS formulation.

no palpable matter in 100 mL of unstirred water kept at 24 ± 1°C.

Tablet preparation

In addition to the compression coated tablets, complete ORS tablets (0·5 g) (Formulations A-O, Table 1) in which coated and uncoated electrolytes were used were also prepared at the same pressure. In all cases the tablets were compressed with an upward movement of 0·68 cm s^{-1}. They were held at the pre-set compression pressure for 30 s.

Moisture absorption of tablets

Tablets were transferred to different relative humidity (RH) environments immediately after preparation and packaging, and stored at 30 ± 1°C. Moisture absorption was assessed by weighing at intervals. Different humidities were achieved following the Table in Weast et al (1986), as before.

Dissolution test

The dissolution patterns of the ORS powders, granules and tablets were assessed by measuring the conductance of electrolytes in solution. The conductance meter[19] was connected to a six-spindle dissolution tester and a recorder. The distilled water (500 mL) in the dissolution vessels was kept at 24 ± 1°C and stirred at 100 rev min^{-1}. Powders, granules (0·5 g) or individual tablets were introduced into the vessel and the change in conductance as the electrolytes went into solution recorded automatically. The lag period and the time taken for 30 and 50% of the electrolyte to go into solution was read from the charts.

Results and Discussion

Moisture absorption

At the lower relative humidity (68·6% RH), all the currently used ingredients (Formula A, Table 1), when individually stored, absorbed little moisture over 120 h. Potassium citrate, and sodium acetate rapidly absorbed moisture, increasing in weight by 50% or more over 24 h. At the higher relative humidity (93%), moisture was absorbed rapidly by potassium citrate, sodium acetate and sodium chloride, and all three had completely dissolved within 24–48 h. Glucose, sodium bicarbonate, sodium citrate and potassium chloride absorbed less than 10% moisture over the same time interval.

Combinations of the powdered ingredients had greater hygroscopicities than that of the most hygroscopic individual component. The effect was more than additive. For example, potassium chloride and sodium citrate powders each absorbed less than 1% moisture after 168 h at 93% RH. Combined in an approximately 2:1 ratio (2·9 sodium citrate: 1·5 potassium chloride), a 40% increase in weight was observed within 48 h and the powdered mixture had gone into solution within 100 h. The presence of glucose in the mixture was not sufficient to prevent the moisture absorption. A combination of the electrolyte components rapidly absorbed water, a pattern closely resembling that of the complete ORS mixture.

Formulations in which potassium citrate or sodium citrate (hydrous or anhydrous) were used absorbed moisture faster than the WHO/UNICEF formula. In addition, there appeared to be an interaction between glucose and the sodium acetate which led to the formation of a wet mass of the ORS mixture within a few hours of mixing. A similar interaction has been noted by de Cespedes (1983) but this interaction was not investigated further.

The presence of trace contamination of sodium chloride by the more hygroscopic salts of magnesium citrate and calcium chloride may partially account for the higher moisture absorption shown by sodium chloride over the other ORS ingredients (Van Campen et al 1980). Moisture absorption by water soluble substances may be better explained in terms of a model that describes the rate of sorption of water vapour on a solid as a function of the relative humidity, RHi, of the environment surrounding the sample. This model was proposed by Van Campen et al (1980, 1983a). It was assumed that water sorbed on a surface dissolves some of the solid to form a saturated solution with a critical relative humidity, RHo, characteristic of the solid. Water would continue to condense on the liquid film as long as RHo is less than RHi and a saturated solution will be maintained. The reported RHo values for potassium chloride, sodium chloride and glucose are 84·3, 75·3 and 81·3, respectively (Van Campen et al 1983b). Thus, at 71% RH these ORS components would absorb less moisture (RHi < RHo). At the higher relative humidity of 93%, the ingredients would absorb moisture, more so for the sodium chloride which has the lowest RHo. Increased hygroscopic behaviour of mixtures has been observed before with mixed fertilizer salts and glues containing sorbitol and glycerol (Adams & Merz 1929; Griffin 1945; Van Campen et al 1980).

Kontyny & Zografi (1985), in their study on the moisture sorption kinetics for water soluble mixtures of solids, reported RHo values for a number of mixtures of alkali halides, sucrose and quaternary ammonium salts. In all cases, the RHo values for the mixtures were less than those of individual components, e.g. RHo values for potassium chloride-sodium chloride were between 65 and 67. Since the difference between RHi would be greater than that of the component with the lowest RHo, moisture absorption of the mixture may be expected to be higher. This behaviour seems to have been confirmed with the mixture of water-soluble ingredients of ORS since intimate mixing of the ORS ingredients, especially the electrolytes, results in a marked increase of hygroscopicity. The preparation of a stable ORS formulation ideally requires avoidance of direct contact of the ingredients with each other and/or protection of the electrolyte component of the formulation from the environment.

Compression characteristics

Sodium citrate and potassium citrate individually gave frail tablets, even at high compression pressures. Potassium chloride, sodium chloride and Emdex were directly compressible, giving hard tablets at low compression pressures. Although hydrous sodium citrate had very good compression characteristics, the anhydrous salt did not readily compress.

Compression of complete ORS formulations gave fragile tablets, Table 2. The addition of dry binders did not improve the compression characteristics.

On its own, glucose powder was not directly compressible at the pressures used. When glucose was granulated with glucose syrup, and there was careful control of both the rate of addition of granulating fluid and drying, tablets could be produced that varied in both crushing strength and disintegration. As the moisture content of the glucose granules decreased with drying, there was a non-linear relationship between moisture content and disintegration time of the resulting tablet. Tablet crushing strength could be increased by increasing the compression pressure.

Direct compression of the present complete ORS mixture, Table 1, is difficult, and this may be accounted for by the large proportion of glucose in the formulation. The use of a commercially available directly compressible glucose such as Emdex may facilitate the preparation of an ORS tablet, although its use may prove too costly for developing countries. However, a compressible glucose granule can be prepared that will readily compress into a rapidly disintegrating tablet.

Table 2. Tablet crushing strength and moisture absorption by various oral rehydration salt mixtures (Table 1).

Formulation	Crushing (kg)* strength	% wt increase after 24 h	
		71% RH	88% RH
A	0·5	0·7	3·3
B†	0·5	—	—
C	1·0	6·2	8·8
D	1·0	4·8	8·9
E	3·3	6·9	11·0

* Compression pressure 214 MPa.

† Poor compression characteristics precluded this from further tests.

Coating of electrolytes

Coating of the moisture absorbing component(s) by Eudragit L caused a decrease in moisture absorption. Coating of granules of a sodium chloride-sodium citrate mixture gave better results than sodium chloride alone. Coating of a mixture of all the electrolytes gave less satisfactory results.

Fig. 1 shows moisture absorption of ORS tablets prepared with and without Eudragit L—coated sodium chloride/sodium citrate granules. A decreased relative moisture absorption rate was observed at the two lower relative humidities. It appears, therefore, that the film coat still retains some of its protective properties after compression but this protection is insufficient at the highest relative humidity.

Simulated compression coating of the electrolytes with either Emdex or granulated glucose produced significant protection, even at high relative humidities, Figs 2, 3. Although this method of protection is evidently technically feasible, compression coating of tablets on the scale needed is a difficult and demanding process. In the environment of a developing nation this approach to the problem may not therefore be entirely realistic. However, with access to the sophisticated equipment needed for production and quality control of a compression coated tablet, an electrolyte core with a glucose coat would be an elegant solution to the stability issue. The commercially available Emdex glucose or

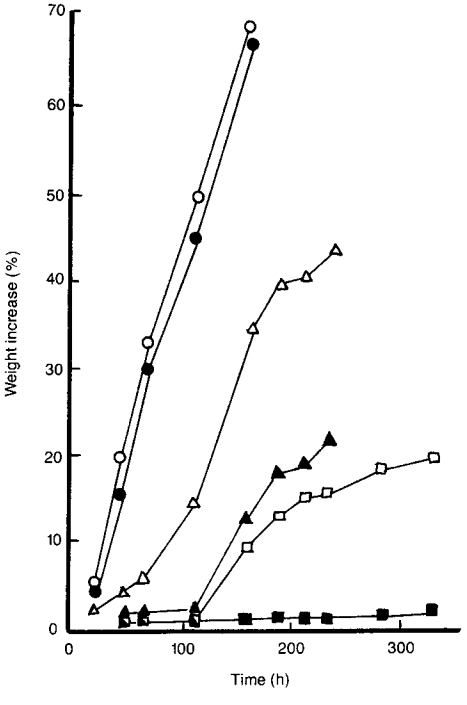

FIG. 1. The effect of Eudragit L coating on sodium chloride/sodium citrate granules in ORS tablet Formulation A, Table 1, stored at 30°C at various relative humidities. Open symbols—uncoated granules, closed symbols—coated granules. □ ■ 68·6% RH. △ ▲ 81·1% RH. ○ ● 92·9% RH.

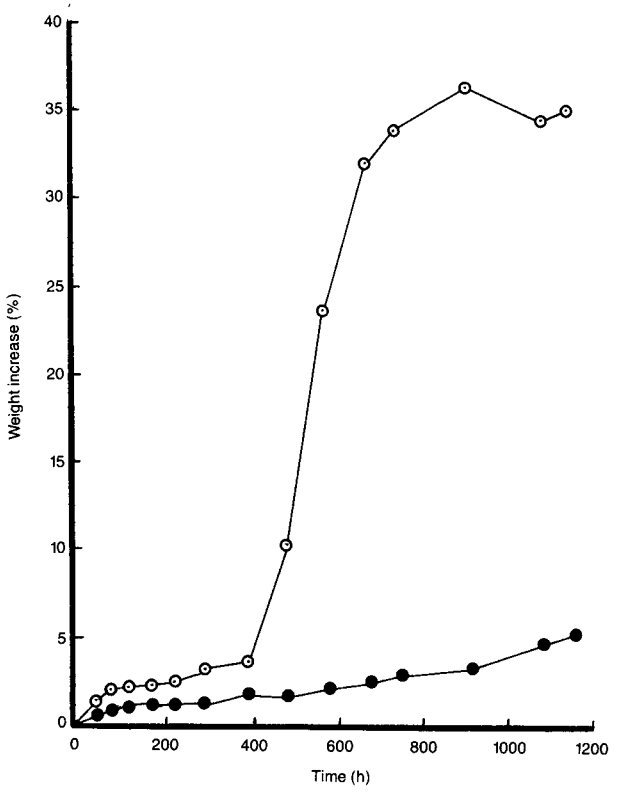

FIG. 2. The effect of high humidity, 68·6% RH at 30°C, on ORS tablets (Formula A, Table 1) prepared with or without protection of the electrolytes. O All components, mixed and compacted. ● Electrolytes compacted to form a core tablet which is compression coated with granulated glucose (see text).

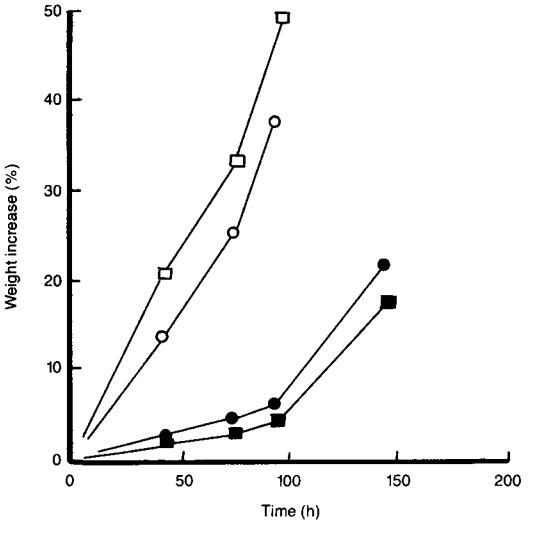

FIG. 3. The effect of high humidity. 92·9% RH at 30°C on protected and unprotected ORS tablets (Formula A, Table 1) using wet-granulated glucose or Emdex direct compression glucose. Open symbols—all ingredients mixed and compacted. Closed symbols—electrolytes compacted to a core tablet which is compression coated with glucose □ ■ Emdex glucose. O ● Wet-granulated glucose.

the prepared glucose granules, wet-granulated under carefully controlled conditions, appear to be broadly equivalent in this context (Fig. 3).

Dissolution and disintegration

Compression coated tablets containing Emdex had appreciably longer dissolution times than formulations using wet granulated glucose (Table 3). The Emdex tablets were harder, reflecting the excellent compression characteristics of this material. Compressed coated core tablets had longer lag periods before the electrolytes dissolved but, once this stage had been reached, the solution rate was not markedly different from uncoated material.

Preliminary formulation experimentation showed that the lag phase could be decreased by adding 10% starch as a disintegrant. However, the simplest solution to the problem of hard tablets, which otherwise have excellent stability to high humidity storage, is to instruct that the tablets be crushed before solution and administration.

Packaging

Tests involving packing 2 × 0·5 g directly compressed solution tablets of the ORS formulation mixtures (unprotected) in heat-sealed minigrip bags suggested that 4 mil polyethylene film provided a high degree of protection up to 93% relative humidity (Fig. 4).

Conclusions

Although the UNICEF ORS formulation is not easily compacted into useful solution tablets, we have demonstrated that separation of the components into glucose and electrolytes will result in an improvement in properties of the tablets, including stability. The electrolytes can be protected from moisture by film coating with a resin, Eudragit L, or by compression coating the electrolytes in a core with the glucose granulated separately. This latter approach provides a hard tablet suitable for transportation under a variety of conditions. Additional protection could be obtained by packing the tablets in sealed bags, 4 mil polyethylene providing excellent protection against 93% relative humidity at 30°C.

Thus, the prospect of an improved accuracy and flexibility of dosage of this important treatment for diarrhoeal dehy-

Table 3. The dissolution times of Emdex compression coated tablets and Eudragit coated electrolyte tablets (dissolution medium water at 37°C, see text).

Material	Time(s) to dissolve contents (by conductivity) 30%	50%
Direct mixture of all ingredients (Formula A, Table I)	15	30
Tablet of all ingredients (above)	115	200
Mixture of glucose and Eudragit coated electrolyte granules	42	65
Tablets of Eudragit coated electrolytes	180	270
Electrolytes compression coated with wet granulated glucose	55	80
Electrolytes compression coated with Emdex glucose	210	280

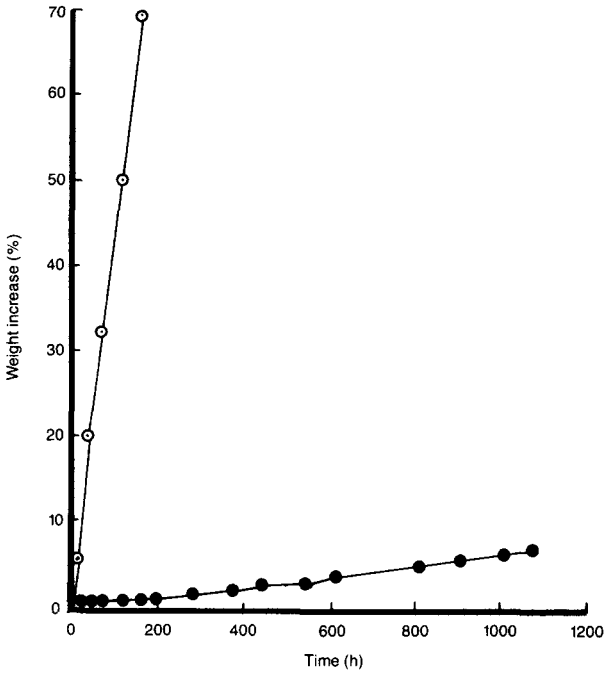

FIG. 4. The effect of storage of directly compressed ORS tablets (Formula A, Table 1) in 4 mil sealed polyethylene bags at 92·9% RH and 30°C. ○ 2×0·5 g tablets stored in an open dish. ● 2×0·5 g tablets in polythene bags.

dration by direct compression of the ingredients into solution tablets would appear to be feasible.

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