IMPROVING THE STABILITY OF A PRODUCT CONTAINING INTER-REACTIVE INGREDIENTS: A COMPARISON OF DIFFERENT APPROACHES

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A syrup granule formulation was found to be insufficiently stable for use in tropical markets. This was shown to be due to an interaction of the drug with sodium methyl-p-hydroxybenzoate, included as a preservative, in the presence of residual moisture from the aqueous granulation process.

Two approaches to prevent the interaction were to separate the drug and the preservative and to lower the moisture content.

The first study, known as the double granule product, was to prepare two groups of granules, one containing the drug and the other the preservative. The granules were mixed together before filling into the bottles.

A further extention of this was the triple granule product which consisted of 10% of drug containing granules and 10% of preservative - containing granules dispersed in plain sugar granules.

To ensure that complete separation of the drug and preservative was achieved a multilayered granule was developed consisting of a core containing drug, a middle layer of sugar and an outer shell containing the preservative and flavours.

The second method of overcoming the stability problem was to reduce the moisture content of the product to below 0.1%. This was achieved by pre-drying the flavour and preservative and then preparing a dry mix of the ingredients with no granulation.

Long term stability data (see table) on the above formulations show that after 2 months at 50°C and 4 months at 37°C the triple granule formulation showed an improved chemical stability compared with the single and double granule products. However, the triple granule was considered to be still unsuitable for tropical markets.

The multilayered granule although showing better stability than the triple granules still showed a poor stability after 2 months at 50°C.

The dry mix formulation has shown the best chemical stability to date.

To investigate whether the improved stability of the dry mix formulation was due solely to its reduced moisture content, stability studies were conducted on samples adjusted to a range of moisture contents. An inverse relationship between moisture content and stability was found. Furthermore, the stability of the dry mix formulation was similar to that of the original granule formulation when both were tested at the same moisture content.

Storage Formulation	Moisture Content	Percentage Initial Drug Content	
		2 Months at 50°C	4 Months at 37°C
Single Granule	0.28%	71.1	86.9
Double "	0.22%	57.5	94.3
Triple "	0.21%	77.4	93.0
Multilayered Granule	0.19%	79.2	98.6
Dry Mix	0.04%	94.8	101.2
" "	0.09%	62.7	99.1
" "	0.14%	65.0	95.0
" "	0.20%	61.5	93.8
" "	0.30%	55.1	90.4