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Calcium sulphate dihydrate: an useful excipient for tablets containing labile actives

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Tablets containing an angiotensin-converting enzyme inhibitor and either calcium sulphate dihydrate or lactose monohydrate as main excipients (fillers) exhibited similar technical properties and stability.

Most angiotensin-converting enzyme inhibitors (e.g. enalapril, moexipril, quinapril, ramipril; hereafter called prils) are inherently prone to degradation in solid dosage forms. The main degradates are diketopiperazine derivatives (DKPs) and prilats. The former arise from an intramolecular nucleophilic attack of the secondary amino nitrogen in the aliphatic chain on the carboxylic acid carbon resulting in expulsion of water, formation of a N−C-bond and cyclization whereas the latter (prilats) are hydrolysis products of the carboxylic ethyl ester vector in the drug molecules (Gu and Strickley 1987). Formation of DKPs may be arrested or minimized for example by adding basic reagents, for instance sodium hydrogen carbonate, to the formulation that transform the carboxylic acid moiety into a carboxylate anion (Gu et al. 1990), and degradation to prilats may be reduced by keeping moisture (water) content as low as possible in the tablets. It has been claimed that excipients belonging to the chemical classes of mono- and disaccharides or sugar alcohols like lactose or mannitol have stabilizing effects on prils in solid dosage forms (Harris et al. 1993).

Calcium sulphate dihydrate ($CaSO_4$, $2H_2O$) is available from Penwest Ltd. as a specially-processed direct compression grade named Compactrol. It is a white or off-white, odourless, non-hygroscopic, free flowing powder, slightly soluble (1 : 375) in water, average particle size 120 μm, bulk density not more than 1.10 g/ml, tapped density 0.90–1.35 g/ml (Moreton 2003). We have found pH approx. 6.8 in a 10% aqueous slurry and loss of drying approx. 0.2% (IR moisture balance, 105 °C) in Compactrol samples.

In oder to investigate the technical properties and stability of pril-containing tablets using calcium sulphate dihydrate (Compactrol) as main excipient (filler) a trial batch was prepared (Formulation C) and for comparison another batch (Formulation L) employing lactose monohydrate. The compositions of these two formulations are displayed in Table 1.

Batch sizes were 8.5 kg = 50,000 tablets (formulation C) and 6.5 kg = 50,000 tablets (formulation L). Mixing and granulation was carried out in an intensive mixer. Following drying at 45 °C to a specified loss of drying of not more than 0.80% (IR moisture balance, 100 °C)

Table 1: Compositions of formulation C (calcium sulphate dihydrate) and formulation L (lactose) (mg/tablet)

	Formulation C	Formulation L
Pril	5	5
Sodium hydrogen carbonate	5	5
Calcium sulphate dihydrate (Compactrol)	141.3	
Lactose monohydrate		96.6
Starch pregelatinized (Starch 1500)	17	19.5
Croscarmellose sodium (Ac-Di-Sol)		2.6
Ethanol (96%)/water purified (1 + 1)	q.s. (38)	q.s. (28)
Sodium stearyl fumarate (Pruv)	1.7	1.3

Table 2: Properties of formulation C (calcium sulphate dihydrate) and formulation L (lactose) tablets

	Formulation C	Formulation L
Average mass (n = 100)	171.0 mg (c.v. 1.1%)	130.5 mg (c.v. 1.4%)
Hardness (n = 20)	36.7 N (c.v. 6.0%)	42.8 N (c.v. 4.6%)
Friability (n = 2)	0.06%	0.07%
Disintegration (n = 3)	2.5 min. (c.v. 9.6%)	2.5 min. (c.v. 11.1%)
Assay	5.00 mg/tablet	4.93 mg/tablet
Dissolution (30 min)	97.5%	100.6%
Diketopiperazine	0.12%	< 0.05%
Prilat	< 0.1%	0.24%

Table 3: Analyses of formulation C (calcium sulphate dihydrate) and formulation L (lactose) tablets after 1 month at 40 °C/75% RH in Al/Al blisters

	Formulation C	Formulation L
Assay	5.00 mg/tablet	5.03 mg/tablet
Dissolution (30 min)	94.0%	98.7%
Diketopiperazine	0.18%	0.06%
Prilat	0.54%	1.40%
Total impurities	0.88%	1.46%

(formulation C; found 0.70%) and not more than 1.3% (formulation L; found 1.05%) and sizing the granulates were blended with the lubricant (sodium stearyl fumarate) and compacted in a rotary tablet press to a target tablet mass of 170 mg (formulation C) and 130 mg (formulation L), diameter 7 mm, circular in both cases. The properties of the tablets are enumerated in Table 2 (the dissolution test was performed in 0.1 N HCl, 900 ml, paddles, 50 rpm).

Tablets from both batches were packaged into aluminium/aluminium (Al/Al) blisters and put on stability trial at 40 °C/75% RH for one month. The results of pertinent analyses are depicted in Table 3.

It is evident from Table 2 that the technical properties of tablets manufactured with calcium sulphate dihydrate (Compactrol) or lactose monohydrate as main excipients (fillers) are similar. Moreover, as seen from Table 3, the stability of both formulations is comparable except that formation of impurities is lower in the calcium sulphate dihydrate tablets. In view of this, the claim concerning special stabilizing effects of disaccharides like lactose on prils in solid dosage forms appears questionable.

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