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Tablets with high lactose content: effects of some binders and disintegrants on their properties

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Tablets containing 91% lactose monohydrate and 4% starch pregelatinized exhibited the best technical properties in comparison to tablets of similar composition with either povidone plus croscarmellose sodium or hydroxypropylcellulose low substituted as binders/disintegrants.

Formulation of tablets with a high lactose content may be desirable due to their low content of unbound moisture when dealing with labile actives. However, in order to accomplish satisfactory properties of the tablets such as hardness, disintegration and dissolution employment of additional excipients like binders and/or disintegrants is necessary in most cases.

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. Tablets with a high content of lactose monohydrate may be appropriate in order to satisfy the latter condition since this excipient typically exhibits only about 0.2% loss on drying when tested with an IR moisture balance at 100 °C.

Table 1: Compositions of formulation PC (2% povidone + 2% croscarmellose sodium), S (4% starch pregelatinized) and H (4% hydroxypropylcellulose low substituted) (mg/tablet)

Formulation	PC	S	H
Pril	10	10	10
Sodium hydrogen carbonate	10	10	10
Lactose monohydrate	455	455	455
Povidone	10		
Croscarmellose sodium (Ac-Di-Sol)	10		
Starch pregelatinized (Starch 1500)		20	
Hydroxypropylcellulose low substituted (L-HPC LH-11)			20
Ethanol (96%)/water purified (1 + 1)	q.s. (78)	q.s. (60)	q.s. (65)
Sodium stearyl fumarate (Pruv)	5	5	5

Table 2: Properties of formulation PC (2% povidone + 2% croscarmellose sodium), S (4% starch pregelatinized) and H (4% hydroxypropylcellulose low substituted) tablets

Formulation	PC	S	H
Average mass (n = 100), mg (cv)	496.8 (1.1)	499.7 (0.4)	502.1 (0.4)
Hardness (n = 20), N (cv)	124 (6.1)	106 (1.7)	112 (4.9)
Friability (n = 2), %	< 0.05	< 0.05	0.5–1.2
Disintegration (n = 2), min.	4.6–4.7	2.5–2.6	1.3
Assay, % of theoretical	98.3	99.0	100.2
Dissolution (after 30 min.), % (cv)	98.0 (1.3)	98.6 (0.8)	99.2 (0.7)
Diketopiperazine, %	0.13	0.10	0.11
Prilat, %	< 0.10	0.14	0.11
Total impurities, %	0.28	0.35	0.22

Remarks: Granulate of formulation PC was very hard with uneven particle size. Granulate of formulation H exhibited filming/picking and capping/lamination on compaction

In oder to investigate the technical properties and stability of pril-containing tablets using lactose monohydrate as main excipient (filler) in a concentration of 91% trial batches were prepared containing 2% povidone (binder) plus 2% croscarmellose sodium (disintegrant) (formulation PC), 4% starch pregelatinized (binder/disintegrant) (formulation S) and 4% hydroxypropylcellulose low substituted (binder/disintegrant) (formulation H). The compositions of these formulations are shown in Table 1.

Batch size was 6.0 kg = 12,000 tablets. 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 (NMT) 0.4% (IR moisture balance, 100 °C) (formulation PC; found 0.31%), NMT 0.6% (formulation S; found 0.21%), and NMT 0.4% (formulation H; found 0.24%) 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 500 mg, diameter 11 mm, circular in all 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).

The tablets 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 low substituted hydroxypropyl-

Table 3: Analyses of formulation PC (2% povidone + 2% croscarmellose sodium), S (4% starch pregelatinized) and H (4% hydroxypropylcellulose low substituted) tablets after 1 month at 40 °C/75% RH in Al/Al blisters

Formulation	PC	S	H
Assay, % of theoretical	96.4	98.0	99.1
Diketopiperazine, %	0.28	0.12	0.22
Prilat, %	0.29	0.64	0.56
Total impurities, %	0.77	0.92	0.90

cellulose are unacceptable due to filming/picking and lamination/capping on compression combined with high friability. The formulation with povidone/croscarmellose sodium furnishes very hard granules with uneven particle size resulting in inferior mass uniformity and rather slow disintegration. Moreover, this formulation exhibits appreciable loss in potency on storage (Table 3). By contrast, the starch pregelatinized formulation furnishes tablets with excellent technical properties.

References

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Effect of *Aralia cachemirica* Decne root extracts on blood glucose level in normal and glucose loaded rats

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An aqueous and alcoholic extract of the roots of *Aralia cachemirica* (Araliaceae) were evaluated for hypoglycemic activity in normal fasted and glucose induced hyperglycemic rats. The aqueous and alcoholic extracts at a dose of 250 mg/kg showed statistically significant ($p < 0.01$) hypoglycemic activity in glucose loaded animals however no effect was observed in normal fasted rats.

Aralia cachemirica (Araliaceae), a lax shrubby herb, 1 to 3 m tall, is found distributed in temperate Himalayas from Kashmir to Sikkim at 2100 to 4000 m altitude (Asolkar et al. 1992). It is known that most of the members in Araliaceae family have high molecular weight polysaccharides (glycans) stored in their roots and many medicinal properties including hypoglycemic activity of these drugs are attributed to these glycans (Tomoda et al. 1985; Fang et al. 1985; Tomoda et al. 1984; Divakar and Bensita 2000). Many *Aralia* species and their isolated constituents show remarkable hypoglycemic activity (Yoshikawa et al. 1996; Martinez and Staba 1984; Yoshikawa et al. 1995). On these basis it was found worthwhile to investigate this plant for hypoglycemic activity. The following phytoconstituents have already been isolated from the plant: octadec-6-enoic acid, 8- primara-14,15-diene-19-oic acid, aralosides A&B (George et al. 1984) Nonane, a hexacosane derivative, petroselinic acid, stigmasterol and β-sitosterol. Anti-inflammatory activity of this plant has also been reported (Asolkar et al. 1992).

The hypoglycemic activity of *A. cachemirica* was evaluated in this study. Both the aqueous as well as the alcoholic extracts showed statistically significant effects ($p < 0.01$) in glucose induced hyperglycemic rats (table) against a control group. However no hypoglycemic activity was observed in normal fasted rats (data not shown).

The results indicate that the roots of *Aralia cachemirica* possess statistically significant hypoglycemic activity and also suggest that the hypoglycemic constituents are present both in aqueous as well as alcoholic extracts. Further studies are in progress to identify the components responsible for hypoglycemic activity.