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Benazepril hydrochloride: effects of particle size on tablet properties

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Tablets manufactured from fine powder (average particle size, D[4,3] = 50.1 μm) benazepril hydrochloride exhibited unacceptable processing and quality properties whereas microcrystalline material (D[4,3] = 4.5–7.7 μm) furnished a product with good processing and quality characteristics.

Benazepril hydrochloride is an angiotensin-converting enzyme inhibitor that has not been described in any pharmacopoeia so far. It is a white to off-white, crystalline powder, freely soluble in water, ethanol and methanol (Belal et al. 2004). Specifically, the water solubility has been stated to be 78 mg/ml (Li et al. 2004). The same paper describes impairment of the dissolution rate of benazepril hydrochloride from tablets containing more than approximately 3.5% moisture as determined by the Karl Fischer method. The present communication reports an unexpected influence of the drug's particle size on processing of tablets and their physical properties.

Benazepril hydrochloride was obtained from two manufacturers, Q and S. The material from Q was microcrystalline (QM) whereas that from S was either fine powder (SF) or microcrystalline (SM). The particle size data by volume for these three materials were as follows (laser light diffraction, Malvern Mastersizer 2000, dispersion 0.1% lecithin in isohexane + ultrasonication for 10 seconds; D[4,3] denotes average particle size):

$$\text{QM } d(0.1) = 2.2\,\mu\text{m},\ d(0.5) = 6.9\,\mu\text{m},\ d(0.9) = 14.2\,\mu\text{m},\ D[4,3] = 7.7\,\mu\text{m}$$

$$\text{SF } d(0.1) = 4.7\,\mu\text{m},\ d(0.5) = 42.4\,\mu\text{m},\ d(0.9) = 107\,\mu\text{m},\ D[4,3] = 50.1\,\mu\text{m}$$

$$\text{SM } d(0.1) = 0.9\,\mu\text{m},\ d(0.5) = 3.6\,\mu\text{m},\ d(0.9) = 9.2\mu\text{m},\ D[4,3] = 4.5\,\mu\text{m}$$

All drug materials were of similar analytical potency/purity and exhibited identical X-ray powder diffraction spectra (Philips PW 1710 instrument, Cu K_α radiation, 1.54 Å, 20 mA, 40 kV).

Composition of tablets: Benazepril hydrochloride 20 mg, lactose monohydrate, starch pregelatinized (Starch 1500), croscarmellose sodium (Ac-Di-Sol) and castor oil hydrogenated (Cutina HR).

Manufacturing method: Granulation with purified water in an intensive mixer followed by drying in a fluidized bed at 45 °C to a specified loss of drying of not more than 1.6% (IR moisture balance, 100 °C), sizing, blending with the lubricant (castor oil hydrogenated) and compaction in a rotary tablet press to a target tablet core mass of 200 mg, 11 × 5.5 mm, oval. The tablet cores were film-coated with an aqueous film-coating suspension consisting of hypromellose, macrogol 8000, titanium dioxide and iron oxides to a target mass increase of 2%. The finished tablets were packaged into aluminium/aluminum (Al/Al) blisters and put on stability trial at 40 °C/75% RH. Two tablet batches were prepared from each drug material.

Table 2: Analytical and stability data (40 °C/75% RH) for finished tablets manufactured from microcrystalline (QM, SM) and fine powder (SF) benazepril hydrochloride

Batch	Time, months	Average mass (n = 20), mg	Hardness (n = 10), N	Disintegration (n = 6), min.	Assay, %	Amount dissolved after 30 min (n = 6), %
QM1	0	206.3	41*	3.5	100.3	99.7
	3	208.5			99.1	
	6	207.7	68	2.4	97.3	92.8
QM2	0	205.4	41*	3.5	101.0	100.2
	3	207.1			97.9	
	6	208.1	65	3.0	96.4	92.8
SF1	0	203.4	99*	11.2	97.3	98.5
	3	203.5	120	16.6	95.3	64.4
	6	203.5	121	16.0	93.3	49.9
SF2	0	206.5	63*	1.0	89.1	91.0
SM1	0	206.3	59*	3.4	98.5	97.0
	3	205.9	90	4.0	97.0	
	6	206.3	92	4.5	96.0	98.0
SM2	0	207.0	67*	3.4	100.5	98.0
	3	206.6	91	4.0	98.5	98.0
	6	206.5	93	4.2	96.5	100.0

* Before film-coating

Table 1: Processing data for tablet cores manufactured from microcrystalline (QM, SM) and fine powder (SF) benazepril hydrochloride

Batch	Batch size, kg	Drug particle size, D[4,3], μm	Amount of granulation liquid, mg/tablet	Granulate loss on drying, %	Flowability of granulate, mm	Compression force, kN	Tabletting speed, tablets/h	Remarks
QM1	30	7.7	41.1	1.1	14	8.9	60,000	No problems
QM2	30	7.7	41.9	1.2	12	9.0	60,000	No problems
SF1	34	50.1	55.9	1.6	6	12.6	100,000	Picking/sticking to punches
SF2	34	50.1	46.4	1.2	14	12.7	50,000	Severe picking/sticking to punches
SM1	34	4.5	41.2	1.0	10	12.6	100,000	No problems
SM2	34	4.5	41.5	1.0	10	12.7	100,000	No problems

The processing data for the tablet cores are outlined in Table 1 (flowability of granulate was determined with a Flodex flowmeter and expresses the minimum diameter of the circular hole required for flow; thus smaller values are better) and analytical/stability data for the finished tablets are depicted in Table 2 (the dissolution test was performed in water, 900 ml, paddles, 50 rpm).

It is evident from Table 1 that the two particle size qualities of benazepril hydrochloride exhibit very different results: the microcrystalline variety furnished good processing properties whereas tabletting of the fine powder form was beset with great difficulties, notably picking/sticking to punches. Moreover, analytical/stability data of tablets (Table 2) containing the fine powder active show unacceptable properties (low assays, variable disintegration times and severe decrease in dissolution on storage). By contrast, tablets manufactured from the microcrystalline active have good quality attributes.

References

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