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Formulation Studies of Furosemide–Amiloride HCl Combination Tablets

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ABSTRACT

During the formulation studies of a furosemide–amiloride HCl combination tablet, an unexpected interaction between the two drugs was encountered. The drugs tended to form aggregates when in contact with the dissolution medium during dissolution testing. This phenomenon decreased the dissolution of both actives significantly. Various formulas were tried to eliminate this problem. Granulation of the formulation with povidone produced a tablet with good dissolution properties. A possible mechanism for preventing the formation of furosemide–amiloride HCl aggregates in the presence of povidone is described.

INTRODUCTION

A fixed combination drug product may be more convenient in patient management than two individual products. For example, a tablet that combines the relative short-acting diuretic furosemide and the potassium sparing but long-acting diuretic amiloride HCl for once a day dosing may have a better patient acceptance than the need to take the two products separately. This combination may provide the required diuretic effect while reducing potassium loss (1). It may also avoid the possible gastrointestinal disturbances associated with potassium supplements (2) if amiloride HCl is not included in the dosing regimen.

During tablet formulation studies, dissolution data showed that the dissolution rates of both actives were lower than expected for the 40 mg furosemide/10 mg amiloride HCl combination tablet. Visual observation revealed that furosemide and amiloride HCl combinations tended to form aggregates when in contact with the dissolution medium. This was believed to be the cause of the reduced dissolution rates.

Since furosemide is a poorly water-soluble drug, dissolution may be a rate-limited step in drug absorption. It has been reported that different formulation variables such as the type of disintegrants (3), binders (4), and processing techniques (3) affected the dissolution as well as the bioavailability of furosemide tablets. The present

study was conducted to better understand the interactions between furosemide and amiloride HCl when dosed together, and to identify formulations which would eliminate the interaction/aggregate formation and allow for rapid dissolution of both active ingredients.

EXPERIMENTAL

Materials

Materials were used as received: furosemide, USP (SIFA Ltd, U.K.), amiloride hydrochroride, USP (Siegeried, Switzerland), sodium starch glycolate, NF (Edward Mendell Co., Carmel, NY), microcrystalline cellulose, NF (FMC Corp., Philadelphia, PA), lactose hydrous, NF (Formost Whey Products, Baradow, WI), starch, NF (A. E. Stanley Manufacturing Co., Decatur, IL), pregelatinized starch, NF (National Starch and Chemical Corp., Bridgewater, NJ), croscarmellose sodium, NF (FMC Corp., Philadelphia, PA), povidone, USP (Plasdone K 29-32, GAF Chemical Corp., Wayne, NJ), and magnesium stearate, NF (Mallinckrodt Inc., St. Louis, MO).

Tablet Preparations

The formulations listed in Table 1 were prepared according to the following methods:

- Formula 1: wet granulation tablet
  Furosemide, amiloride HCl, and excipients were blended and granulated with water. The wet granulation was dried at 50°C. The dried granulation was screened through a No. 20 mesh screen. The lubricant was added and mixed uniformly. The tablets were compressed using 7.94 mm standard concave tooling to a target hardness of 7–9 kp.
- Formula 2: Direct compression tablet
  All the ingredients were mixed thoroughly and compressed into tablets according to the method described above.
- Formula 3: Formulation prepared by wet granulation of furosemide and then blended with amiloride HCl
  Furosemide and excipients were uniformly blended and granulated with water. The wet mass was dried at 50°C. The dried mass was prescreened through a No. 20 mesh screen. Amiloride HCl and the lubricant were added and mixed thoroughly. The tablets were then compressed as described above.
- Formula 4: Formulation prepared by a mixture of single active granulations of furosemide and amiloride HCl
  The wet granulations were prepared separately for furosemide and amiloride HCl by blending the drug and half quantities of excipients, and following the formulation procedures

Table 1

Formulations of 40 mg Furosemide/10 mg Amiloride HCl Tablets

Ingredients	Milligrams/Tablet					
	Formula 1	Formula 2	Formula 3	Formula 4	Formula 5	Formula 6
Furosemide USP	40.00	40.00	40.00	40.00	40.00	40.00
Amiloride HCl USP[a]	11.24	11.24	11.24	11.24	11.24	11.24
Sodium starch glycolate NF	7.00	7.00	9.00	12.60	12.60	9.00
Microcrystalline cellulose NF	40.90	40.90	16.00	16.00	16.00	16.00
Lactose hydrous NF	51.76	51.76	62.90	73.26	73.26	75.51
Starch NF			21.30			
Pregelatinized starch NF	6.30	6.30	7.40	6.00	6.00	
Croscarmellose sodium NF	2.00	2.00				
Povidone USP, K 29-32						7.45
Magnesium stearate NF	0.80	0.80	0.80	0.80	0.80	0.80

[a]All formulations were prepared to contain 10 mg amiloride HCl on an anhydrous basis. Amiloride HCl USP contains 11–13% moisture.

described above. The two dried granulations were then blended, lubricated, and compressed as described previously.

- Formula 5: Bilayer tablet
  The active granulations were prepared as described in Formula 4, and separately lubricated and compressed into bilayer tablets using the tooling described above.
- Formula 6: Formulation prepared by wet granulation using povidone as a binder
  The actives and excipients were mixed and granulated with povidone solution. The remainder of the methods were the same as those for Formula 1.

Dissolution Procedure

All dissolution tests were performed by using USP method II, rotated at 50 rpm in 900 ml of phosphate buffer (pH 5.8) at 37°C. Initial samples of 5 ml were taken at 45 min. For the infinity-time samples, the paddle speed was increased to 250 rpm, after initial sampling, for 20 min, then the speed was reduced to 50 rpm for the sample taking. The samples were filtered through a 0.45-μm filter.

The samples were analyzed by a high-performance liquid chromatograph (HPLC) method using a Waters Detector (Model 450) at 361 nm. A Zorbax C8 column and a mobile phase consisting of triethylamine/acetonitrile/water (0.2/810/1200), pH adjusted to 2.4 with phosphoric acid, were used. The retention times were 2.5 min for amiloride HCl and 3.5 min for furosemide at a flow rate of 1.5 ml/min.

The reported dissolution rates for each formulation represent an average of 6 individual tablets.

RESULTS AND DISCUSSION

The dissolution rates of various tablet formulations are shown in Table 2. All the dissolution testing was conducted in pH 5.8 phosphate buffer solution. This medium is used for the furosemide tablet dissolution specified in the USP/NF monograph (5).

The Formula 1 tablets contain commonly used excipients and were prepared by a conventional wet granulation process. The dissolution rates of both actives were found to be unexpectedly low. Similar formulations containing 40 mg furosemide/2.5 mg amiloride HCl and 40 mg furosemide/5 mg amiloride HCl exhibited acceptable dissolution rates (6). For these formulations, both actives gave greater than 90% dissolution at 45 min. On further investigation, it was found that an aggregation of two actives formed at the 40 mg furosemide/10 mg amioride HCl level. The presence of the excipients was unable to eliminate this occurrence. The remaining formulations were an attempt to reduce or eliminate this interaction between the drugs to allow for rapid dissolution of both components.

The direct compression tablet formulation (Formula 2) did not improve the dissolution. In theory, this manufacturing process is designed to break the tablet into primary particles for quick dissolution. The advantage of direct compression is the optimization of tablet disintegration, in which each primary drug particle is liberated from the tablet mass and is available for uninhibited dissolution.

Formula 3 was an attempt to separate furosemide from amiloride HCl by preparing a furosemide granulation and then adding amiloride HCl powder prior to tableting. No improvement in dissolution was observed even though the tablets disintegrated quickly. It seems furosemide aggregated with amiloride HCl immediately after it was liberated from the disintegrated granules.

Table 2

Dissolution Rates of 40 mg Furosemide/10 mg Amiloride HCl Tablets

Active	Time	Average % Dissolved (of label claim) ± *SD*					
		Formula 1	Formula 2	Formula 3	Formula 4	Formula 5	Formula 6
Furosemide	45 min	51 ± 11	64 ± 8	36 ± 1	34 ± 4	77 ± 6	104 ± 3
	Infinity[a]	89 ± 2	77 ± 3	67 ± 1	92 ± 4	92 ± 4	103 ± 2
Amiloride HCl	45 min	45 ± 7	69 ± 12	26 ± 3	27 ± 4	90 ± 1	102 ± 2
	Infinity[a]	75 ± 4	87 ± 4	67 ± 4	82 ± 4	99 ± 1	102 ± 1

[a]Infinity: after 45 min at 50 rpm, speed was increased to 250 rpm for 20 min.

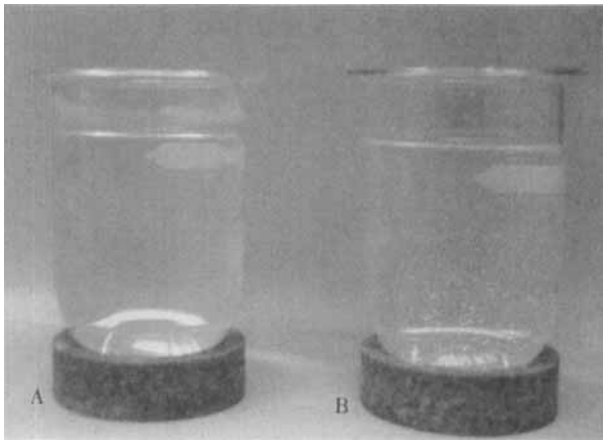

Figure 1. Agglomeration of furosemide and amiloride HCl in pH 5.8 phosphate buffer. A, furosemide 40 mg, amiloride HCl 11.24 mg, and povidone K29-32 7.45 mg. B, furosemide 40 mg and amiloride HCl 11.24 mg.

Separation of these two drugs was attempted by individually granulating the drug and then mixing for tableting (Formula 4). However, no improvement in dissolution was found with this technique.

Separation of the two drug granulations, as in the bilayer tablets (Formula 5), seemed to prevent some of the aggregation. An improvement in the dissolution was observed.

The tablets of Formula 6 were prepared by using povidone as a binder. The dissolution rates for both actives in the tablet were 100% at 45 min.

In order to see what the difference was that produced the good dissolution results in Formula 6, povidone was dry blended with furosemide and amiloride HCl powders. This mixture was placed into the dissolution medium and slightly agitated to disperse the powder to see if the combination would agglomerate as previously noted. No agglomeration occurred [Figure 1(A)]. Figure 1(B) shows the formation of aggregates of the drug when no povidone was added.

Doherty and York (7) studied the furosemide–povidone interaction in solution by proton nuclear magnetic resonance. Their studies revealed that the sulfonamide proton in the furosemide molecule interacts with povidone through hydrogen bonding. With the presence of povidone in the drug mixture, the interaction between furosemide and povidone may reduce the hydrogen bonding potential of furosemide with amiloride HCl in the dissolution medium. This apparently prevents the aggregation of the drugs and promotes rapid dissolution.

CONCLUSION

A tablet formulation of furosemide and amiloride HCl with good dissolution properties was developed. Although bioavailability is an important parameter in the comparison of new drug combination tablets, it is important to formulate a tablet with good dissolution to ensure uninhibited availability.

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REFERENCES

1. S. G. Brooks, R. B. Christie, J. Roche, H. P. Fainhead, D. Muirhend, H. A. Townsend, and H. L. Shaw, Curr. Med. Res. Opin., 9, 141 (1984).
2. F. G. MacMahon, J. R. Ryan, K. Abedamar, and A. Ertran, Lancet, 2, 1059 (1982).
3. M. H. Rubinstein, Drug Dev. Ind. Pharm., 6, 105 (1980).
4. M. H. Rubinstein and J. M. Rughams, Drug Dev. Ind. Pharm., 4, 541 (1978).
5. *The United States Pharmacopeia*, 23, National Formulary 18, 1995, p. 697.
6. P. C. Sheen, personal data.
7. C. Doherty and P. York, J. Pharm. Sci., 76, 731 (1987).