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Short Communication

Formulation of Furosemide Dispersible Tablets for Use in Paediatrics

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Furosemide (4 mg) dispersible tablets tailored for paediatric patients were formulated by direct compression using granulated lactose as the filler. Combinations of superdisintergrants namely sodium starch glycolate-crospovidone, sodium starch glycolate-croscarmellose and croscarmellose-crospovidone were incorporated to form three tablet batches; with a total superdisintegrant concentration of 4% w/w per tablet. The quality of the resultant tablets was evaluated using pharmacopoeial physicochemical tests. Tablets prepared with sodium starch glycolate-crospovidone and croscarmellose-crospovidone as superdisintegrants were found to comply with all specifications for tablet quality, while those formulated with sodium starch glycolate-croscarmellose, failed both the uniformity of weight and friability tests. This study showed that low dose furosemide dispersible tablets for pediatric use can be formulated using 4% w/w combinations of sodium starch glycolate-crospovidone and croscarmellose-crospovidone as superdisintegrants.

Keywords: Furosemide, dispersible tablet, pediatric, formulation, superdisintegrants

INTRODUCTION

Furosemide, known chemically as 4-chloro-*N*-furfuryl-5-sulphamoylanthranilic acid, is a loop diuretic that is primarily used in the management of oedema secondary to renal, hepatic and/or cardiovascular disease in both adults and children. In paediatrics, furosemide has also been used 'off label' in management of bronchoconstriction related to chronic lung diseases, in hydrocephalus and in some diagnostic procedures [1, 2]. Compounding of medications, particularly those initially indicated for adult use, is often necessary in pediatric pharmacy practice due to lack of age-appropriate dosage forms and/or strengths for children [3]. According to the list of human pharmaceutical products registered in Kenya [4], the only oral furosemide preparations available locally are 40 mg strength tablets which are unsuitable for children. Frusol, a furosemide oral solution is available commercially on the global market however furosemide dispersible tablets have not been formulated before. A recent study on oral medications compounded for pediatric patients at Kenyatta National Hospital between January, 2012 and December, 2013 [5], revealed that furosemide suspensions were the second most frequently compounded medication further highlighting the need for development of an age-appropriate pediatric formulation locally.

The formulation of age-appropriate medicines for paediatrics is an evolving research area due to recognition of the risks associated with compounding. Liquid dosage forms, traditionally the most

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favorable dosage form for children, are challenging to formulate due to the moisture sensitive nature of most active pharmaceutical ingredients, bulk, as well as being prone to dosing inaccuracies. These factors explain the paradigm shift towards the development of flexible solid dosage forms such as dispersible tablets, which can be converted to a liquid dosage form at the time of administration for paediatrics [6]. Dispersible tablets are formulated to disperse rapidly, within three minutes, in a small amount (~10 ml) of fluid.

The formulation of dispersible tablets relies on the use of superdisintegrants which ensure rapid tablet disintegration at lower concentrations (2-5% w/w tablet composition) than traditional disintegrants. Synthetic superdisintegrants, that include croscarmellose, crospovidone and sodium starch glycolate, defer in their mode of action, charge, compressibility and gelling nature on interaction with water, which are some of the factors that govern the choice of superdisintegrant/s for a particular formulation [7].

The aim of the current study was to formulate a 4 mg dispersible furosemide tablet suitable for pediatric patients, whose furosemide posology is 1-2 mg/kg body weight [1, 2]. The effect of the different combinations of three superdisintegrants croscarmellose, crospovidone and sodium starch glycolate, on tablet manufacturability and quality were investigated.

EXPERIMENTAL

Materials

Furosemide, lactose, starch, croscarmellose, crospovidone, sodium starch glycolate, colloidal silicon dioxide, talc and magnesium stearate were kind donations from Laboratory and Allied Limited, Kenya. All materials used were of pharmaceutical grade. Furosemide USP reference standard, solvents and buffers for assay/dissolution studies were obtained from Drug Analysis and Research Unit, School of Pharmacy, University of Nairobi.

Compatibility studies

Previous studies on drug-excipient compatibility by Granero et al. revealed that the excipients chosen for the development of this formulation were compatible with furosemide [8].

Preparation of granules

Lactose granules were prepared by wet massing lactose powder using 10% starch binder, prepared as a paste with water as the granulating fluid. The granules were air-dried for 20 h, screened and sized to obtain granules with a diameter of 250-500 μm.

Preparation of tablets

Tablets were prepared by direct compression. Furosemide, colloidal silicon dioxide (glidant), croscarmellose/ crospovidone/sodium starch glycolate (superdisintegrants), talc and magnesium stearate (lubricants) were added to the prepared lactose granules (filler) at concentrations shown in Table 1 and blended to produce three formulation batches (F1, F2 and F3). Compression of the blends was then carried out using an Erweka, electric type, single punch tablet press, type 1 EP 1, Germany, with a set target tablet weight of 500 mg. The batches were prepared in triplicate with batch sizes of 240-300 tablets.

Table 1: Composition of furosemide 4 mg strength tablets

Tablet ingredients (% w/w)	F1	F2	F3
Lactose granules	93.6 %	93.6 %	93.6 %
Furosemide	0.8 %	0.8 %	0.8 %
Sodium starch glycolate	2 %	2 %	-
Crospovidone	2 %	-	2 %
Croscarmellose	-	2 %	2 %
Colloidal silicon dioxide	0.1 %	0.1 %	0.1 %
Talc	1 %	1 %	1 %
Magnesium stearate	0.5 %	0.5 %	0.5 %

Evaluation of tablet quality

The tablet quality was evaluated using physical tests (appearance, uniformity of weight, hardness, friability and disintegration) and chemical tests (assay and dissolution). Only the tablet batches that passed the physical tests were subjected to chemical tests.

Uniformity of weight

Twenty individual tablets were weighed using a top loading balance (KERN 440-43N), the average tablet weight determined and the deviation of each tablet weight from the average calculated. The BP specifies that for tablets weighing more than 250 mg no more than two tablets should deviate from the average tablet weight by 5% [9].

Hardness

A Schleuniger-2E electronic hardness tester was used to measure the force required to fracture ten individual tablets diametrically. The limits for the tablet hardness test were set at between 5-11 kPa.

Friability

Twenty randomly selected tablets were dusted then weighed before being placed into an Erweka drum friabillator. The drum friabillator (Erweka, Heusenstamm kr. Offenbach/main, type TA3R, West Germany) was set to run for 100 revolutions after which tablets were dusted, reweighed and percentage weight loss determined. The BP specification of 1% was used as the limit for tablet friability [9].

Disintegration

Six individual tablets were placed in 10 ml of water and the time taken for complete disintegration determined. The BP specification for dispersible tablets of 3 min at room temperature was used as the limit [9]. This was a simplified method based on WHO methods to test the disintegration of dispersible tablets [10].

Assay

Twenty tablets were powdered and an amount equivalent to 25 mg furosemide diluted with a 70:30:1 water: acetonitrile: glacial acetic acid mixture to produce a 1 mg/mL furosemide sample [11]. A standard of similar concentration was prepared. Furosemide content in the sample and standard solutions was assayed by HPLC on Shimadzu HPLC System (Sil-20AHT Prominence auto sampler, Shimadzu, Japan) using a Lunar column (250 mm×4.6 mm, 5 um).

Dissolution

Dissolution was carried out using 900 mL of pH 5.8 phosphate buffer at 37°C in USP apparatus type 2. The apparatus was set to run for 1 h at 50 rpm, with samples being withdrawn at intervals of 15 min [11] and furosemide content analysed by HPLC.

RESULTS AND DISCUSSION

Three batches (F1, F2 and F3) of dispersible furosemide tablets were prepared and evaluated for their physical properties (Table 3) as well as assay for furosemide content and dissolution profile (Table 3).

Appearance

The prepared tablets were circular, white in colour with smooth shiny faces and tablet diameters of ~5 mm. No visible tablet defects were noted.

Uniformity of tablet weight

As shown in Table 2, tablet batches F1 and F3 passed the uniformity of weight test, with no more than two tablets deviating from the average tablet weight by 5%. The average tablet weight for batches F1 and F3 was ~500 mg. Tablet batch F2 which had an average tablet weight of 479 mg failed the uniformity of weight test. This observation is interesting considering that the tablet formulation was similar with the only batch difference being the type of superdisintegrant used. Tablet batch F2 was prepared using anionic superdisintegrants sodium starch glycolate and croscarmellose, while tablet batches F1 and F3 were prepared using combinations of a non-ionic and anionic superdisintegrant.

Table 2: Physical properties of prepared furosemide tablets

Tablet batch	F1	F2	F3
Uniformity of weight	Complied	Non-compliant	Complied
Average tablet weight (mg)	501 ± 8	479 ± 12	502 ± 8
Tablet hardness (kPa)	6.3 ± 2.2	5.9 ± 0.6	6.4 ± 1.3
Tablet friability (%)	0.9	2.6	0.9
Tablet disintegration (sec)	62	137	69

Hardness

Although tablet hardness is a non-compendial test, it acts an early indicator of possible issues with friability. A hardness level that can strike a balance between mechanical strength and ease of disintegration is usually set in-house. The three tablet batches were all found to comply with the set hardness of 5-11 kPa (Table 2) [12].

Friability

As shown in Table 2, tablet batches F1 and F3 passed the friability test with tablet weight loss of less than 1%. Tablet batch F2, prepared using sodium starch glycolate and croscarmellose superdisintegrants, failed the friability test with a tablet weight loss of 2.6%.

Disintegration

Tablets from the three batches were found to disperse rapidly (within 3 min) in 10 ml of water to give a white suspension (Table 2). Tablet batches F1 and F3 which passed all the physical tests were subjected to assay and dissolution tests.

Assay

Tablet batches F1 and F3 complied with the USP specification for furosemide content, with tablets containing 90-110% of the stated label claim (Table 3).

Dissolution

The USP specifies that on tablet dissolution, not less than 80% of the labeled amount of furosemide should be released after 60 minutes. As shown in Table 3, both tablet batches F1 and F3 complied with this specification. However the high relative standard deviation observed on tablet dissolution, predicts poor content uniformity. Indeed attaining acceptable content uniformity is a challenge with low dose tablets (such as the 0.8% w/w furosemide tablet in the present study), and it is recommended that a smaller tablet, with the API comprising a higher percentage of final tablet weight, be manufactured.

Table 3: Evaluation of prepared furosemide tablets for content and dissolution profile

Tablet batch	F1	F2	F3
Assay (%)	101.0 ± 0.2	ND	108.8 ± 1.0
Dissolution (%)	95 ± 16.1	ND	82 ± 16.3

ND = not determined

CONCLUSION

Low dose furosemide dispersible tablets formulated using combinations of sodium starch glycolate-crospovidone and croscarmellose-crospovidone as super-disintegrants complied with compedial physico-chemical specifications for quality. The minimum tablet weight that could be compressed by the tablet press used was 500 mg. Thus tablets of 500 mg were prepared, though a smaller tablet weight of approximately 100 mg would be desirable considering the low concentration of furosemide (4 mg) per tablet. Further optimization of these formulations, such as inclusion of taste masking agents to improve palatability, is recommended.

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