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Current Pharmaceutical Analysis, 2016, *12*, 000-000

Enhancement of Dissolution Rate of Furosemide Using a Solid Dispersion with D-Glucosamine HCl

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Abstract: Furosemide is a potent high ceiling (loop) diuretic mainly used in the treatment of edematous states associated with cardiac, renal, and hepatic failure, and the treatment of hypertension. Furosemide has been classified as a class IV drug as per the biopharmaceutical classification system (BCS). D-Glucosamine HCl was used to increase the aqueous solubility of furosemide. The objective of the present work is to improve de dissolution profile of furosemide by formation of a physical mixture and a solid dispersion with D-glucosamine HCl. The solid dispersion was prepared by solvent method using acetone/water. The dissolution properties and physicochemical properties of furosemide: D-glucosamine HCl physical mixture and solid dispersion were investigated by dissolution test, X-ray diffractometry, infrared spectrometry, differential scanning calorimetry (DSC), microscopy (SEM) and ^{35}Cl Nuclear Quadrupole Resonance (NQR). The diuretic activity was proved comparing the solid dispersion with pure furosemide. This study shows that the dissolution rate of furosemide can be enhanced considerably by formulating it with D-glucosamine HCl, as a physical mixture or as a solid dispersion although cristallinity was maintained. Solid dispersion and pure furosemide showed significant increase in diuresis in rats as compared to the control group.

Keywords: Furosemide, D-Glucosamine HCl, solid dispersion, physical mixture, dissolution profile, diuretic activity.

1. INTRODUCTION

Furosemide, 4-chloro-2-[(2-furanylmethyl)-amino]-5-sulfamoylbenzoic acid, (pKa 3.6) (PubChem CID: 3440) is a potent high ceiling (loop) diuretic mainly used in the treatment of edematous states associated with cardiac, renal, and hepatic failure, and the treatment of hypertension. It is known to exist in five forms of modifications (three polymorphs and two solvates) [1]. Furosemide has been classified as a class IV drug as per the biopharmaceutical classification system (BCS) [2]. Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has meant a challenge when developing a suitable formulation for oral administration [3]. The main possibilities to improve dissolution are: a) to enlarge the surface area available for dissolution by dimishing the particle size; b) to allow surfactant systems solubility; c) to make water soluble complexes; d) to use of pro drug derivatization approach such as strong electrolyte salt forms that usually have higher dissolution ratios; e) manipulation of the solid state of the drug substance to improve drug dissolution by decreasing crystallinity of the drug substance through formation of solid solutions [4-12]. The most effective method for improving dissolution is the use of solid dispersion technique but this is reliant on optimization of carrier and solvent. Solid dispersion is defined as the dispersion of one or more active ingredients in inert carriers at solid state and can be prepared by fusion, solvent, or solvent-fusion methods. In the solid dispersions, the particle size is reduced to submicron size or to molecular size. This particle size reduction generally increases the rate of dissolution. In same samples, the drug is altered from crystalline to amorphous form, which increases solubility [7, 13].

A number of investigations demonstrate that the formation of solid dispersions of furosemide with various excipients can significantly increase its in vitro dissolution rate [1, 14-18]. Shin, Patel and co workers [15-17] reported disappearance of crystallinity in the solid dispersions prepared. Chaulang, De Zordi and coworkers [1, 18] suggest that part of the drug structure may have been converted to the amorphous state, and this probably explains why the dissolution of the drug was increased in the solid dispersions prepared.

D-Glucosamine HCl (PubChem CID: 71306816) is highly water soluble, non toxic compound that when given orally, has been shown to decrease pain and improve mobility of

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1573-4129/16 $58.00+.00

osteoarthritis joints of humans, which has led to its popular use as a nutritional supplement in both humans and dogs. Glucosamine is a monosaccharide and is a weak base. Due to its instability, the hydrochloric or sulfate salts area used in therapy. It was used to increase the aqueous solubility of carbamazepine [7], piroxicam [19] and ibuprofen [20]. Gluconolactone was also used to increase the solubility of carbamazepine [21]. The objective of the present work is to improve the dissolution profile of furosemide developing a physical mixture and a solid dispersion with D-glucosamine HCl. The solid dispersion was prepared by solvent method using acetone/water. The dissolution properties and physicochemical properties of furosemide: D-glucosamine HCl physical mixture and solid dispersion were investigated by dissolution test, X-ray diffractometry, infrared spectrometry, differential scanning calorimetry (DSC), microscopy (SEM) and ^{35}Cl Nuclear Quadrupole Resonance (NQR). The diuretic activity was proved comparing the solid dispersion with pure furosemide.

2. MATERIALS AND METHODS

2.1. Materials

Furosemide (purity 99.9 %) was purchased in Saporiti, Argentina and Glucosamine HCl (purity ≥ 99.0 %) was from Sigma-Aldrich, USA, and were used without further purification. Acetonitrile used was of HPLC grade, Sintorgan (Buenos Aires, Argentina) and dibasic potassium phosphate AR Grade, J. T. Baker (Estado de Mexico, Mexico). Distilled water was passed through a 0.45 µm membrane filter. All the solvents and reagents used were of analytical or HPLC reagent grade.

2.2. Preparation of Solid Dispersion and Physical Mixture

Solid Dispersion Prepared by Solvent Evaporation

A mixture of 5 g of furosemide and D-glucosamine HCl (1:1) by weight respectively was wetted with acetone: water (2:1 ratio) The solvent was evaporated under reduced pressure at 40°C, and the resulting residue was dried under vacuum for 3 h, stored in a dessicator at least overnight, ground in a mortar, and passed through a # 80 sieve. The mixture was analysed by HPLC before use.

Physical Mixture

A physical mixture having the same weight ratio as described in solid dispersion was prepared by thoroughly mixing appropriate amount of furosemide and D-glucosamine HCl in a mortar until a homogeneous mixture was obtained. The resulting mixture was sieved through a # 80 sieve. The mixture was analysed by HPLC before use.

2.3. Analysis of the Active Ingredient

The liquid chromatographic method was carried out on a Phenomenex Spherisorb 10 µm RP-18 200 x 4.6 mm and detection was performed at 235 nm. The mobile phase consisted of 0.02M dibasic potassium phosphate buffer: acetonitrile (80:20 v/v) run at a flow rate of 1 mL/min and maintained at room temperature. The chromatographic separation was obtained with retention time of 10.0 min. The injection volume was 20 µL. The HPLC system consisted of a dual piston reciprocating Thermo Finnigan pump, a Rheodyne injector, a DAD Dionex Ultimate 3000 with operating software Chromeleon 6.8 was used during the study.

2.3.1. Preparation of Standard Solution

An accurately weighed quantity of 50 mg of furosemide was dissolved in 50 mL of ethanol. Pipette out 2 mL of the resulting solution in a 100 mL volumetric flask. The volume was made with mobile phase (Conc 20 µg/mL). The solutions were passed through a 0.45 µm nylon membrane filter before injection (25 mm disposable filter; Cat. N° R04SP02500 Osmonics Inc., Minnesota, USA).

2.3.2. Sample Preparation

Approximately 100 mg of the solid dispersion or the physical mixture were weighed exactly, placed into a 50 mL volumetric flask, taken to volume with ethanol. Pipette out 2 mL of the resulting solution in a 100 mL volumetric flask. The volume was made with mobile phase (Conc 20 µg/mL).The solutions were passed through a 0.22 µm nylon membrane filter before injection (25 mm disposable filter; Cat. N° R04SP02500 Osmonics Inc., Minnesota, USA).

2.4. Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (DSC 822, Mettler Toledo, Switzerland) was used for thermal analysis of drug and excipient. Individual samples (drug and excipient) as well as the physical mixture of the drug and the excipient were weighed directly in the pierced DSC aluminum pan and scanned in the temperature range of 30-350 °C under atmosphere of dry nitrogen (99.99% purity, flow rate 50 mL min^{-1}). A heating rate of 10 °C/min was used and the obtained thermograms were observed for any interaction. The DSC cell was calibrated with indium (m.p. 156.6 °C; ΔH_{fus}=28.5 Jg^{-1}) and Zinc (m.p. 419.6) as standards. Empty aluminium pans were used as references. Samples with mass 1-2 mg were employed, by duplicate. Data were treated with STARe software Ink. (Mettler Toledo, Switzerland).

2.5. Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra (4000-400 cm^{-1}) for the furosemide test systems were recorded on a Nicolet iS10 FT-IR spectrometer Thermo Scientific. Solid samples were placed over a diamond attenuated total reflectance (ATR) accessory (Smart iTR), without any grinding or KBr. The spectra were collected with 32 scans, at 4 cm^{-1} resolution.

2.6. Nuclear Quadrupole Resonance (NQR)

For NQR measurements, the samples did not need a specific preparation. The material container is a glass cylinder of 2 cm in length and 1 cm in diameter. ^{35}Cl NQR measurements were done using a Fourier transform pulse spectrometer with a Tecmag NMR kit II multi nuclei observe unit and a Tecmag Macintosh-based real time NMR station. The line shape was obtained using spin-echo Fourier transform mapping spectroscopy [22]. The measurements were made upon the echo using the standard two pulse sequence (π / 2 - 70μ - π).

2.7. X-ray Diffraction (XRD)

Powder X-ray diffraction patterns were collected at RT using a D8 Advance X-ray diffractometer (Bruker AXS, Germany). The target was Copper-tube ((Cu Kα radiation λ = 1.5418 Å) and a post-diffraction graphite monochromator. The X-ray generator was set at a voltage of 40 kV and current of 40 mA. Samples were subject to PXRD analysis in step mode with a step size of 0.05º 2θ and a step time of 3 s over an angular range of 2-50º 2θ. The sample holder was rotated in a plane parallel to its surface at the speed of 30 rpm during the measurements. Obtained diffractograms were analyzed with DIFFRAC plus EVA diffraction software.

2.8. Scanning Electron Microscopy (SEM)

Electron micrograph of furosemide, D-glucosamine HCl, physical mixture and solid dispersion were obtained using scanning electron microscope (SEM) Carl Zeiss Σigma at the Laboratorio de Microscopía y Análisis de Rayos X (LA-MARX) of the National University of Córdoba. The samples were sputtered with gold using a Balzers model SDC 030. Micrographs with different magnifications were recorded to study the morphology of the samples.

2.9. Dissolution Rate Studies

Dissolution studies were performed using USP (37) Apparatus 2 (Vankel, VK 7010). The pure drug, the physical mixture and the solid dispersion were placed in capsules N° 0. Tests were carried out with twelve units and were performed at 50 ± 1 rpm. Dissolution media was 0.2M phosphate buffer pH 5.8 at 37 ± 0.5 °C. Dissolution media volume was 900 ml. In all experiments, 10 ml sample aliquots were withdrawn at 5, 15, 30, 45 and 60 min using syringes. All samples were filtered through blue ribbon filter paper. The amount dissolved was calculated by determining the absorbance of an appropriately diluted solution at 276 nm.

2.10. Diuretic Activity

The method of Kau *et al*. (1984) [23], with modification was employed in the determination of diuretic activity. Male Sprague Dawley rats weighing 220-250 g were used. They were fed laboratory diet ad libitum and allowed free access to drinking water and kept in 12 h/12 h light–dark cycle at 22 °C. The animals were fasted overnight, with free access to tap water only. All animals were given an oral loading of normal saline (2% bw). Subsequently, Control group was given 10 mL/kg of normal saline by oral route (p.o.). Other groups received furosemide (pure) or furosemide (solid dispersion) at doses of 10 mg/kg and 30 mg/kg, p.o. All doses were prepared in the same volume in order to ensure that each animal received the similar volume of liquids. Immediately after administration, the animals were placed in metabolic cages (one animal per cage), specially designed to separate urine and feces. The urine, collected in graduated vials, was measured at 1, 2 3 4 5 and 24 h and expressed as mL. Urine electrolytes (sodium, potassium and chloride) were determined by an indirect potentiometric method.

The experiments were carried out following international guiding principles and local regulations concerning the care and use of laboratory animals for biomedical research.

3. RESULTS AND DISCUSSION

3.1. Differential Scanning Calorimetry (DSC)

The furosemide exhibited a simple, sharp exothermic peak that resulted from decomposition of furosemide at temperature of 222.84 °C. D-glucosamine HCl exhibited two endothermic peaks at temperature of 209.77 °C and 225.85 °C. The physical mixture exhibited endothermic peaks at 203.27 °C, 210.26 °C and an exothermic peak at 205.15 °C corresponding both to D-glucosamine HCl and furosemide respectively, although the peak corresponding to furosemide is minor. The solid dispersion showed an endothermic peak at 209.92 °C. The melting exotherm of furosemide was well retained in the blend with D-glucosamine HCl whereas the single exothermic peak of furosemide was not shown in the solid dispersion, this could be considered to correspond to the disappearance of crystallinity or the furosemide is in solid solution inside the D-gluosamine HCl matrix (Fig. **1**).

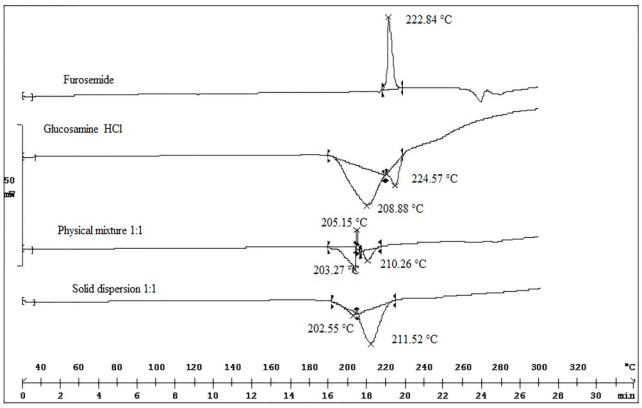

Fig. (1). DSC of Furosemide, D-Glucosamine HCl, 1:1 Furosemide-D-Glucosamine HCl physical mixture and 1:1 Furosemide-D-Glucosamine HCl solid dispersion.

The enthalpy value of the solid dispersion is reduced to half the sum of the endotherms of D-glucosamine HCl and the exotherm of furosemide. Variations in the enthalpy values for the binary mixtures can be attributed to some heterogeneity in the small samples used for the experiments (3-4 mg) [24].

3.2. Fourier Transform Infrared Spectroscopy (FTIR)

Pure furosemide FT-IR spectra showed sharp characteristic peaks at 3398 and 3282 cm^{-1} (SO_2NH_2), 3350 cm^{-1} (NH), 1668 cm^{-1} (COOH) and 1318 and 1140 cm^{-1} (SO_2). The above characteristic peaks appear in the spectra of the physical mixture and the solid dispersion at the same wave number indicating no interaction between the drug and the carrier.

3.3. Nuclear Quadrupole Resonance (NQR)

The normalized NQR spectra of the ^{35}Cl nucleus in the Furosemide molecule are shown in (Fig. **2**). The spectrum of pure Furosemide (Fig. **2A**) could be fitted by two Lorentzian peaks (dashed line) with equal area. Furosemide presents a conformational disorder [25], therefore, each Lorentzian

peak corresponds to molecules with the furan ring in one of the two equilibrium positions. The same area of the peaks indicates similar number of both conformers.

The NQR spectrum of the physical mixture sample (Fig. **2B**) is similar to that observed in pure Furosemide. However, it is possible to observe a widening in the Lorentzian peaks which is probably owing to the stresses introduced in the sample by the preparation method.

Fig. (**2C**) shows that the NQR spectrum of the solid dispersion sample is similar to the above spectra. Only a narrowing of the two Lorentzian peaks is observed; this effect could be due to a reduction of impurities and stress in the sample by means of the recrystallization process.

3.4. X-ray Diffraction (XRD)

Fig. (**3**) shows the X-ray diffractograms for the furosemide, D-glucosamine HCl, physical mixture, and solid dispersion. The pure furosemide showed the characteristics diffraction peaks at 2θ of 6.0, 12.0, 18.1, 18.9, 21.3, 22.9, 24.8, and 28.6º etc., indicating the presence of crystalline furosemide, polymorphic form 1 with triclinic (P-1) crystal structure.

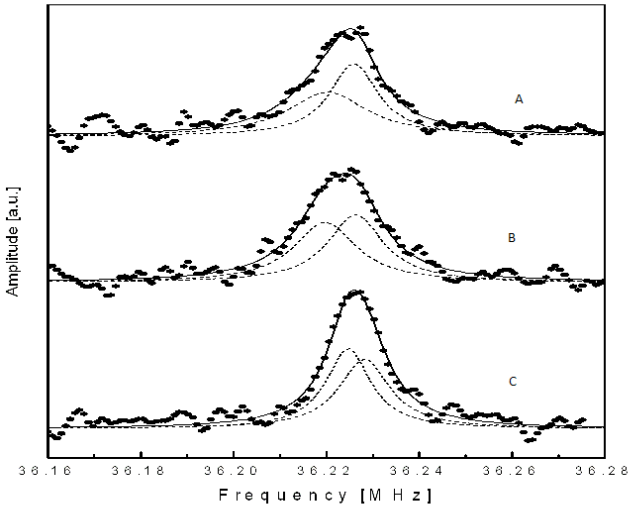

Fig. (2). NQR spectra of 1:1 Furosemide-D-Glucosamine HCl test preparation. Key: a) Furosemide; b) physical mixture; c) solid dispersion.

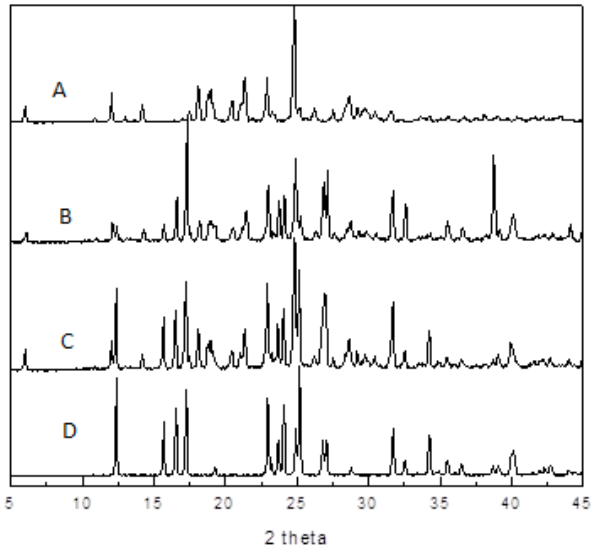

Fig. (3). X-ray diffractograms of 1:1 Furosemide-Glucosamine HCl test preparation. Key: A, Furosemide; B, physical mixture; C, solid dispersion; D, D-Glucosamine HCl.

The pure D-glucosamine HCl showed the characteristics diffraction peaks at 2θ of 12.4, 15.7, 16.5, 17.3, 23.0, 23.7, 24.1, 24.9, and 25.3º etc., indicating the presence of crystalline D-glucosamine HCl, with monoclinic ($P2_1$) crystal structure.

The physical mixture (PM) also showed crystallinity, due to the presence of crystalline furosemide and D-glucosamine HCl. Thus, the mere presence of D-glucosamine HCl in the physical mixture should not interfere with the characterization of coexisting furosemide. The X-ray diffraction pattern of PM was a superimposition of each component.

In case of the 1:1 ratio furosemide-D-glucosamine HCl solid dispersion (SD) also showed crystallinity, and the X-ray diffraction pattern of SD was a superimposition of each component.

3.5. Dissolution Rate Studies

The effect of D-glucosamine HCl on the dissolution of furosemide was investigated for furosemide test preparations. The pure drug was dissolved approximately 41% in this condition. The dissolved amounts of furosemide from the 1:1 furosemide -D-glucosamine HCl physical mixture increased 13% compared with the pure drug. The furosemide-D-glucosamine HCl (1:1) solid dispersion increased dissolved amount in 33% compared with the pure drug (Fig. **4**).

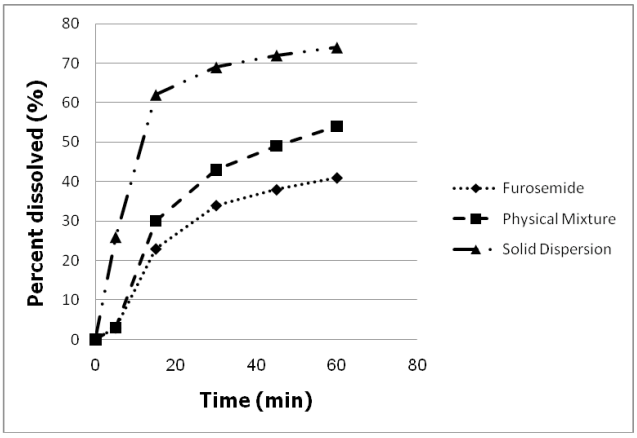

Fig. Dissolution profiles.

3.6. Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) (Fig. **5**) shows the angular crystalline nature of pharmaceutically available furosemide (Fig. **5A**) having individual crystals with length of ~ 10 µm or less whereas D-glucosamine HCl has prismatic shape (polygonal) (Fig. **5B**) and these two different crystal shapes can be easily identified in the physical mixture (Fig. **5C**). It was observed that the solid dispersion sample ob-

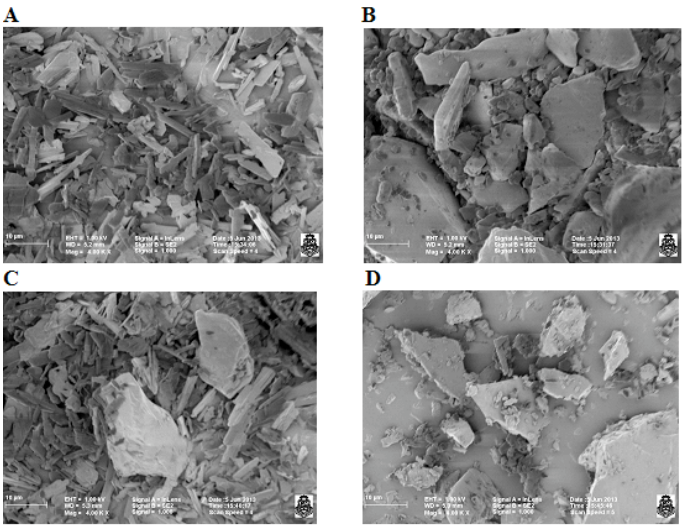

Fig. (5). Photographs (SEM of 10 μM) Key: **A**, Furosemide; **B**, D-Glucosamine HCl **C**, physical mixture; **D**, solid dispersion.

tained from acetone:water (2:1) contained several needle shaped crystals alongside other crystal shapes (Fig. **5D**). The presence of tiny needles of furosemide crystals may be responsible for the improvement in dissolution rate of furosemide in the solid dispersions.

3.7. Diuretic Activity

Oral administration of solid dispersion increased the urinary flow. Solid dispersion significantly increased the urinary output from two hours and continuously throughout the whole analyzed period. The cumulative urinary excretions at 24 h after treatment with solid dispersion 10 mg/kg and 30 mg/kg were 8.9±1.2 and 13.3±3.3 mL, respectively. These values were significantly higher when compared to the control group (5.3±0.8 mL). The cumulative urinary volume was not any different from the diuresis obtained in animals treated with furosemide (pure) (Fig. **6A**, **B**).

The quantity of the urinary sodium, potassium and chloride was measured in samples collected after 5 hours of the oral treatment as shown in (Fig. **6C**). Furosemide (pure and solid dispersion) showed higher concentrations of the electrolytes when compared to the control group.

CONCLUSION

The solid dispersion of furosemide and D-glucosamine HCl was prepared using solvent evaporation. The physical mixture was prepared by thoroughly mixing appropriate amount of furosemide and D-glucosamine HCl in a mortar until a homogeneous mixture was obtained. This study shows that the dissolution rate of furosemide can be enhanced considerably by formulating it with D-glucosamine HCl, as a physical mixture or as a solid dispersion although cristallinity was maintained. The use of a hydrophilic excipient results in greater wetting and increased surface area (reduction of the particle size). During the dissolution studies, it was noted that the solid dispersion sank immediately, while the pure drug kept floating on the surface of the dissolution media. These could be the reasons of the increase of the dissolution rate in the solid dispersion. Solid dispersion and pure furosemide showed significant increase in diuresis in rats as compared to control group, although there was no significant difference between them. The solid dispersion increased the solubility of furosemide and maintained its pharmacological activity.

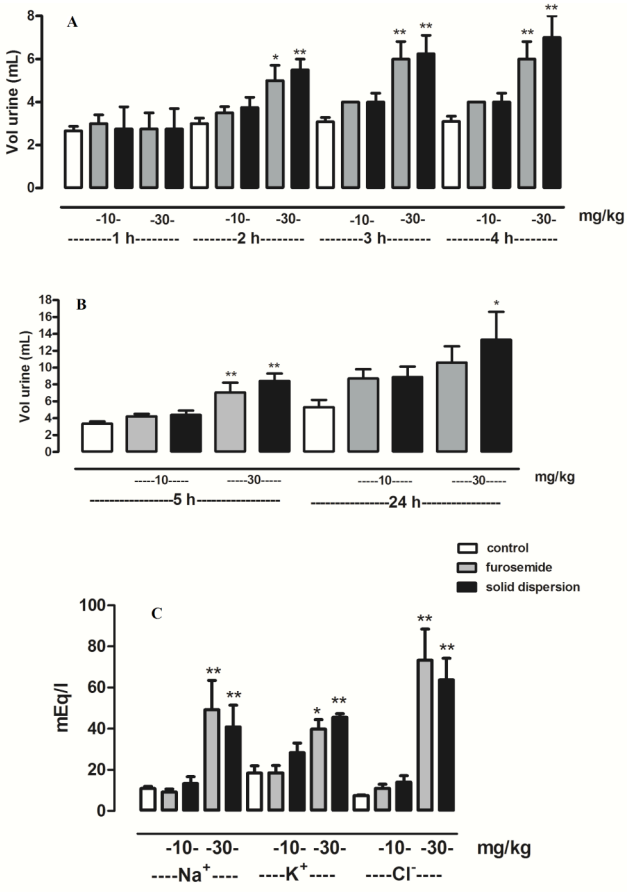

Fig. (6). Diuretic effect of a single oral administration of furosemide, raw material and solid dispersion. **A** and **B**: Urinary output (mL) at doses of 10 and 30 mg/Kg, **C**: Sodium, potassium and chloride levels in urine after administration of furosemide. The electrolytes were reported in the urine collected for 5 h. The results show the mean±SEM of five animals per group. *P<0.05, **P<0.01 compared to control group.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by grant 20020130100342BA to A. I. Segall from UBA and PIP Nº: 11420110100380 from CONICET.

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Received: June 11, 2015 Revised: August 10, 2015 Accepted: August 17, 2015