Compatibility and stability of polygeline (Haemaccel) with different drug products

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Abstract: Compatibility and stability of the polygeline-based blood plasma expander/plasma substitute Haemaccel with different drug products i.e., Profenid, Stemetil, and Lasix were examined in the context of its potential use in surgical, spinal, septic shock and in circulatory insufficiency, because treatment, safety, acceptability and efficacy of drug product may be affected by drug instability or incompatibility. Therefore, drug stability and compatibility are critical elements in accurate and appropriate delivery of drug therapy to patients. This study was initiated to specifically and critically assess the compatibility of Haemaccel with different drug products with the aim of delivering safe, suitable, acceptable and efficacious administration of two different drug products simultaneously in emergency conditions. All of these different brands of drug products were physically and chemically compatible with Haemaccel and all of the test results were almost similar before and after mixing different drugs in Haemaccel. This study revealed that Lasix, Profenid and Stemetil can be administered/co-administered with Haemaccel safely. Different drug product must be studies in detail before it's co-administration with Haemaccel.

Keywords: Haemaccel, ketoprofen, prochlorperazine mesylate, furosemide, compatibility, acceptability.

INTRODUCTION

Plasma substitutes play a key role in fluid therapy in hypovolemia particularly and effectively in intensive care patients and also in emergency (Beards *et al.* 1994; Edwards *et al.* 1988). Therefore, their compatibility and incompatibility information with other drug products is necessary in severe and emergency conditions or treatment prior to co-administration with other drug products.

The compatibility of plasma substitute or plasma Expanders with different drug products has been investigated in previous studies. For example, Haemaccel may be mixed with other infusion solution such as 0.9% sodium chloride injection, Glucose injection and Ringer's Solution/injection or with Heparinised blood, Plasma, Gammaglobulin and other water soluble drug such as Corticosteriods, muscle relaxants, Barbiturates, Vitamines, Streptokinase, antibiotics of Penicillin series, Adrenal cortical hormones, L-nor adrenaline, 6 methyl prednisolone, Anaesthetics, Oxytocin, Cortisone. Moreover, Haemaccel is a recommended infusion fluid for Frusemide and may be used as carrier for insulin (Kraegen *et al.* 1975; Vinik *et al.* 1975; Campbell *et al.* 1976; Hannan & Stathers 1976; Seveso 1963).

Plasma substitutes are also known to be chemically and physically incompatible with many other drug products for example Haemaccel should not be administered with citrated blood. When Vancomycin injection was administered with modified fluid gelatin solution (Haemaccel and Gelofusine), a white precipitate formed immediately (Taylor & Hornbrey 1991). Succinylated gelatin (Gelofusine) can't mix with human blood, Plasma or Plasma fraction. A high incidence or an increased risk of renal failure was observed in patients co-administered Haemaccel and gentamicin (Schnerider *et al.* 1996). The interaction between digoxin and Haemaccl, which contains calcium ions may enhance Digoxin toxicity (Product Information 1999). The present study was initiated to specifically and critically asses the compatibility of Hamaccel with different drug products with the aim of delivering safe, acceptable and efficacious administration of two different drug products simultaneously in severe and emergency conditions. As drug stability and compatibility are critical elements in accurate and appropriate delivery of drug therapy to patients & its potential use in surgical, spinal, septic shock and in circulatory insufficiency.

MATERIALS AND METHODS

Material

In this research/study three different drug products, Profenid (Sanofi) B.No. E005, Stemetil (sanofi) B. No. E014 and Lasix (Sanofi) B.No. N009, were each mixed with Haemaccel brand no. E015, E025, N014 and E019 (Sanofi-aventis) and tested for compatibility at room temperature (25°C) (table 1). A pH meter WTW 525 (Wissenschaftich-Technische Werkstätten, Germany) was used for measuring pH during compatibility studies of Haemaccel. Free amino groups were assessed using a Mettler DL40RC Memo Titrator and a WTW 525 pH meter. The relative viscosity of Haemaccel was determined at 35±1°C using an Ostwald viscometer

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(capillary viscometer, Schott AG, Germany). Total nitrogen was determined by the Kjeldahl method using a Buchi 426 digestion unit and Buchi 339 distillation unit during studies. Electrolytes were detected by a previously calibrated flame photometer PFP7 (Jenway, England) against freshly prepared standard solution. A PCLM3 chloride meter was used to measure chloride. The content of different drug products after mixing in Haemaccel was determined by Spectrophotometer model NICOLT Evolution 300B, USA.

Methods

The following physical and chemical parameters were evaluated before and after mixing: appearance, pH, viscosity, free amino groups, nitrogen content and electrolytes. Spectrophotometric readings were also taken to determine the drug content before and after mixing. The different branded products Profenid, Stemetil and Lasix distributed for marketing containing from 1 ml to 2 ml solution were used. All glassware and utensils were cleans with chromic acid and then rinsed with distilled water. Before starting the compatibility studies, all relevant instruments were cleansed, and calibrated for accuracy.

After mixing the drug products in Haemaccel, the appearance was assessed visually for signs of precipitation or other evidence of alteration such as turbidity or haziness, changes in color, effervescence or evolution of gas and formation of immiscible liquid layers. A WTW 25pH meter used for measuring pH before and after mixing drug products in Haemccel. The relative viscosity of Haemaccel was determined before and after mixing the drug at 35±1^{o}C using an Ostwald Viscometer (Capillary viscometer SCHOTT). The flow rates of 5 ml distilled water and then 5 ml Haemaccel were determined respectively.

Free amino groups were assessed using a Metler DL40 RC Memotitratar and a WTW 525 pH meter. In this test mixture of 40 ml Haemaccel and 1.6ml 2N hydrochloric acid was titrated up to pH 6.00 using 0.2 N Sodium Hydroxide. The quantity of sodium hydroxide consumed (M_1) was recorded, then 4ml of formaldehyde solution (Merck) previously adjusted up to pH 7.00±0.02 was added. The pH value fell sharply after 1 minute. The titration was continued titrate up to pH 8.50 and the consumption of sodium hydroxide (M_2) before and after mixing drug was recorded. Free amino groups was calculated using the formula:
(M_2-M_1)/5 F=ml of 1N sodium hydroxide/40 ml of Haemaccel, where F is factor of sodium hydroxide.

Total nitrogen was determined by Kjeldahal method using a Buchi 426 digestion unit and a Buchi 339 distillation unit before and after mixing of drug products in Haemaccel. Haemaccel (1ml) plus concentrated Sulphuric acid (15ml) (Merck) and one kjeldahl tablet, batch no. TP707758 (Merck, Germany) were digested for 30 minutes at 650°C in Digestion unit. After digestion, sample was cooled and titrated, using distillation unit. Before titrating sample, the pH electrode in the distillation unit was calibrated using buffer solution pH 4, batch no. OC354850 and buffer solution pH 7, batch no. OC354838.

Electrolytes were detected by a previously calibrated flame photometer PFP7 (Jenway, England) against freshly prepared standard solution. The preparation of test and standard solution was as follows. The sample/test solution was 1ml Haemaccel in 100ml of distilled water before and after mixing drug products in Haemaccel. To prepare the standard solution 1000ppm 3.34ml of Na^{+}, batch no. FINA4HI (Jenway, England), 1000ppm 0.20ml of K^{+}, batch no. FIK2LI (Jenway, England) and 1000ppm 0.25 ml Ca^{++}, batch no. FKA12MI (Jenway, England) were mixed in a 100ml volumetric flask and made up with distilled water.

A PCLM3 Chloride meter was used to measure chloride. Calibration and determination of Chloride was as follows: 5ml acid buffer solution, batch no. 1273 (Jenway, England), 10ml distilled water and 0.3ml or 10 drops of Gelatin solution, batch no 2237 (Jenway, England) were placed in a plastic beaker with a stirrer bar and the beaker was placed on the instrument plate form. The 20µl range was selected and 20µl of a standard solution of Chloride 100m mol/l, batch no. 0250135CI (Jenway, England) was added and conditioning was performed. After conditioning a further 20µl standard solution was added and then titrated the reading was closed to 100mmol/l. After calibration the whole process was repeated in the same way, except 20µl Haemaccel was added instead of standard solution and the readings were recorded before and after mixing drug product.

The content of different drug products after mixing in Haemaccel was determined by spectrophotometer model NICOLT Evolution 300BB, USA, in comparison with freshly prepared reference standard solution. The samples were tested with assay methods.

Determination of content of profenid (Ketoprofen) after mixing in haemaccel

For assay determination spectrophotometer was used, after turn on the instrument by power switch, gave warm up time for 10 minutes.

First run blank determination and then run test sample in comparison with freshly prepared reference standard of Ketoprofen B. no. 0513567503 Aventis Pharma, France, for determination of assay. In this study Profenid 2ml injection was used, First of all detected reading of Haemaccel, which was 0.001 nm. The standard and test sample were then investigated as follows. For standard:

0.004g, of reference standard Ketoprofen for Profenid 2 ml injection was placed in 100ml methanol, from that solution pipetted out 1ml into a 100ml volumetric flask, and 1ml 0.02N Hcl was added and made up with methanol. The finding was recorded at 258nm UV light. Test samples, Profenid 2ml injection was added to 500ml Haemaccel, then1 ml was pipetted and dissolved in 100 ml of methanol. From that solution1ml was pipetted out into100ml volumetric flask, and 1ml 0.02N Hcl was added and made up with methanol. Reading was recorded at 258 nm UV light.

Determination of content of stemetil (Prochlorperazine mesylate) after mixing in Haemaccel

First run blank determination and then run test sample in comparison with freshly prepared reference standard of Prochlorperazine mesylate B. no. 062378, Aventis Pharma, for determination of assay. In this study Stemetil 2ml injection was used, First of all detected reading of Haemaccel, which was 0.001nm. The standard and test sample were then investigated as follows. For standard: 0.001g, of reference standard Prochlorperazine mesylate for Stemetil 2ml injection was placed in 100ml ammonical ethanol (1% v/v solution of 0.88 ml ammonia in ethanol), and mixed well, from that solution pipetted out 5 ml into a 200ml volumetric flask, and made up with ethanol. The finding was recorded at 258 nm UV light.

Test samples, Stemetil 2 ml injection was added to 500ml Haemaccel, then 10ml was pipetted and dissolved in 100 ml of ammonical ethanol and mixed well. From that solution 5ml was pipetted out into100 ml volumetric flask, and made up with ethanol. Further from that solution 10ml was pipetted out into100ml volumetric flask, and made up with ethanol. Reading was recorded at 258 nm UV light.

Determination of content of lasix (Furosemide) after mixing in haemaccel

First run blank determination and then run test sample in comparison with freshly prepared reference standard of Furosemide B. no. E531 Aventis Pharma, for determination of assay. In this study Lasix 2ml injection was used, First of all detected reading of Haemaccel, which was 0.001nm. The standard and test sample were then investigated as follows. for standard: 0.00018g, of reference standard Furosemide for Lasxis 2ml injection was placed in 200ml of 0.1N Sodium hydroxide, from that solution pipetted out 5ml into a 100 ml volumetric flask, and made up with 0.1N Sodium hydroxide. The finding was recorded at 271nm UV light. Test samples, Lasix 2ml injection was added to 500ml Haemaccel, then 3 ml was pipetted and dissolved in 200ml of 0.1N Sodium hydroxide from that solution 5ml was pipetted out into100 ml volumetric flask, and made up with 0.1N Sodium hydroxide. Reading was recorded at 271nm UV light.

RESULTS

Compatibility results

All the different brands of drug products were physically and chemically compatible with Haemaccel and all the test results were similar before and after mixing drugs in Haemaccel (tables 2-5). Different studies also confirmed compatibility of Haemaccel with different drug products (3-7). The appearance of Haemaccel remained the same after mixing the different brands of drug products. There was a slight reduction in the pH value of Haemaccel after mixing Stemetil (7.33 to 7.29), Lasix (7.33 to 7.30), except in profenid that was slightly increased (7.26 to 7.28). The viscosity of Haemaccel was similar before and after addition of Stemetil, Lasix, except after addition of Profenid when it increased slightly from 1.78 to 1.79 (table 5).

Similarly, free amino groups increased slightly after addition of profenid (0.556 to 0.578). On other hand free amino group slightly decreased (0.537 to 0.535) when Stemetil is added in Haemaccel and free amino group remain same in case of Lasix (0.536 to 0.536). Nitrogen value either increased in profenid (6.43 to 6.55) or decreased value in stemetil (6.20 to 5.31) and in Lasix (6.22 to 5.37) after addition.

Electrolyte values were almost similar before and after mixing, except for Ca^{++} in Stemetil, which was decreased (6.5 to 6.3) and in Profenid, which was increased (5.5 to 5.6). Chloride values were also the same except for a slight increased (145 to 148) after addition of Profenid and decreased after addition of Stemetil (144 to 143) (table 3).

The spectrophotometry results showed that the content of the drug was almost unchanged after mixing with Haemaccel. There is not any significant change observed after mixing of Lasix in Haemaccel, except decreased value of nitrogen content (from 6.22 to 5.37). Therefore, it might be concluded, that Laxis is compatible with Haemaccel. Since different scientists such as Jasti and coworkers have also been reported compatibility of Lasix with different drug products (26). There is significant change in nitrogen content observed in Stemetil (6.20 to 5.31). On other hand profenid shows slightly change in free amino group (0.556 to 0.578), nitrogen (6.43 to 6.55) and in Chloride (145 to 148). On a whole they are considered as compatible with Haemaccel.

DISCUSSION

As there is a lack of compatibility data/study of the majority of drug products used for co-infusion/co-administration with plasma substitutes in critically ill patients in intensive care units. They require multiple medications therefore this study was carried out to

determine whether mixing different brands of drug products such as, Lasix, Profenid and Stemetil in Haemaccel would alter the physical and chemical parameters of the Haemaccel. For this purpose various different parameters (pH, relative viscosity, free amino groups, nitrogen content and electrolytes) were considered. The results demonstrated negligible changes after mixing. Previous studies (Kraegen *et al.,* 1975; Vinik *et al.,* 1975; Campbell *et al.,* 1976; Hannan & Stathers 1976; Seveso 1963). Regarding compatibility, have indicated that Haemaccel can be infused and used as a carrier solution for different drug products such as insulin, corticosteroids, antibiotics, streptokinase and urokinase, or with glucose, saline, Ringer's solution, heparinised blood and plasma. On other hand Martin in 1986 reported development of skin necrosis (necrotic blister) after administration of two haemaccel-insulin infusions. He recommended caution in use of haemaccel as a carrier solution for insulin therapy (Martin 1986). But haemaccel has ability to reduce adsorption of insulin on to plastic infusion sets (Kraegen *et al*., 1975). Haemaccel is also suitable as a solvent for cefotaxime sodium for intra-arterial treatment of infected ischaemic lesions because its physicochemical properties, such as pH, viscosity and colloid osmotic pressure, resemble those of plasma. By contrast, hetastarch is incompatible with furosemide, streptokinase and insulin.

In the same way, cephalosporins, such as cefotaxime sodium, are not compatible with hetastarch because small crystals have been found to form immediately after mixing, which persist for 4 hours (Wohlford & Fowler 1989). Other cephalosporins drug products, like cefamandole, cefoperazone, cefoxitin, cefazolin and cefalothin are incompatible with hetastarch. The aminoglycosides gentamicin, tobromycin and amikacin are also incompatible with hetastarch (Wohlford & Fowler 1989; Koshiro & Fujita 1983). Gentamicin is also reported to be incompatible with Haemaccel because of an increased risk of renal failure observed (Schnerider *et al.,* 1996).

Although these are all antibiotics, some other antibiotics such as the penicillin series, i.e., carbencillin, cloxacillin and oxacillin, are compatible with both hetastarch and Haemaccel (Fisch *et al.,* 1997; Trissel 1988). Dextran, plasma substitute, is also reported to be compatible with cloxacillin sodium, enalaprilat and famotidine but not compatible with amoxicillin because there was a 9, 12 and 12% loss of amoxicillin sodium at 10, 20 and 50g/l respectively in 1 hour at 25°C in Dextran (Trissel 1988). Its incompatibilities may also arise from the slightly acidic pH of the preparations (Sweetman 2005). Dextran is incompatible with streptokinase and aminoglycoside.

When hetastarch 6% in sodium chloride 0.9%, was mixed with cefotaxime sodium 20mg/ml in dextrose 5% in water, immediate formation of small crystals was observed, which persisted for 4 hours (Wohlford & Fowler 1989).

Viscosity may also affect the compatibility and stability of different drug product and Haemaccel. Siragusa (16) demonstrated that increased viscosity makes an emulsion more stable. Hetastarch has a viscosity of 4.5 kg.m-1.s-1 and Haemaccel 1.23 kg.m-1.s-1 or Pa.s.

There are three types of hetastarch: HES 450, HES 200 and HES 40, which have mean molecular weights of 450,000, 200,000 and 40,000 respectively. The molecular weight of Haemaccel ranges from 30,000 to 35,000. It is possible that higher molecular weights affect the solubility and compatibility. Side groups in the polypeptide bonds of Haemaccel contain a number of reactive groups, i.e., amino, hydroxyl and carbonyl groups/carboxyl groups, (Schöne 1969) which are capable of reaction with other functional groups of different drug products. In this study it is possible that these groups reacted with functional groups of different drug products, which has also amino and carboxyl groups. Drug product has protein-binding ability. The active ingredient of Haemaccel is polygeline, which is a polypeptide manufactured from bovine gelatin. Gelatin is a degradation product of collagen, which is a simple protein, i.e., an albuminoid. Albumin microspheres are biodegradable particles that have excellent pharmaceutical stability and good biocompatibility; these particles have therefore been investigated clinically for the intra-arterial delivery of chemotherapeutic agents; (Fujimoto *et al.,* 1985) they also allow incorporation and sustained release of a variety of drugs (Gupta & Hung 1989).

In present study compatibility of Haemaccel with Lasix (Furosemide) revealed that not only content of Furosemide almost remained the same but also Haemaccel itself remained stable after mixing with Furosemide. Furosemide like other loop diuretics, are bound to plasma protein such as albumin, so it is possible that Furosemide bound with Haemaccel, since Haemaceel is also protein in nature. Danilo and coworkers reported the co-administration of albumin and Furosemide in patients with nephritic syndrome (Danilo 1999). As Furosemide contain carboxyl groups like Haemaccel. Therefore, it is possible that these both group react with each other.

Furosemide has been found to be unstable in acidic media but, very stable in basic media, since Haemaccel has pH range from 7.00 to 7.60 which is basic media. Furosemide can usually be mixed with infusion solutions that are neutral or weakly basic (pH 7 to 10) and with some weakly acidic solutions that have a low buffer capacity. Solutions such as sodium chloride 0.9%, Ringer's injection and dextrose 5% in water have been recommended (Trissel 1988).

Table 1: Different brands of drug products used for the study.

No.	Brand	Weight	Batch No.	Manufacturer
1	Lasix	20 mg/2 ml	N009	Sanofi aventis
2	Profenid	100 mg/2 ml	E005	Sanofi aventis
3	Stemetil	12.5 mg/1 ml x 2	E014	Sanofi aventis
4	Haemaccel	500 ml	E015	Sanofi aventis
5	Haemaccel	500 ml	N014	Sanofi aventis
6	Haemaccel	500 ml	E025	Sanofi aventis

Table 2: Spectrophotometry readings (nm) showing content of different drug product before and after mixing with Haemaccel.

S. No.	Drug Name	Appearance Before and after mixing of drug	Haemaccel Alone	Drug Standard	Haemaccel and drug	Drug content of mixture
1	Profenid	Pale yellow, same	0.001	0.021	0.022	0.021
2	Lasix	Pale yellow, same	0.001	0.008	0.008	0.007
3	Stemetil	Pale yellow, same	0.001	0.035	0.037	0.036

Table 3: Chemical compatibility of haemaccel with stemetil drug's products: Haemaccel B. No. E025 and stemetil1ml B. No. E014.

S. No	Test	Result		Limit
		Before mixing of drug	After mixing of drug	
1.	Appearance	Clear, yellowish Solution.	Clear, yellowish Solution.	Clear, yellowish Solution.
2.	pH	7.33	7.29	7.00-7.60
3.	Viscosity (Relative)	1.78	1.78	1.70-1.80
4.	Free Amino Group	0.537	0.535	0.50-0.65 ml of 1N NaOH/40 ml of
5.	Nitrogen	6.20	5.31	6.0-6.6 mgN/ml.
6.	Sodium	148	148	139-152 m.mol/l.
7.	Potassium	5.1	5.1	4.6-5.6 m.mol/l.
8.	Calcium	6.5	6.3	5.5-7.0 m.mol/l.
9.	Chloride	144	143	130-160 m.mol/l.

Table 4: Chemical compatibility of haemaccel with lasix drug's products: Haemaccel B. No.N014 and lasix 2ml B. No. N009.

S. No	Test	Result		Limit
		Before mixing of drug	After mixing of drug	
1.	Appearance	Clear, yellowish Solution	Clear, yellowish Solution	Clear, yellowish Solution.
2.	pH	7.33	7.30	7.00-7.60
3.	Viscosity (Relative)	1.79	1.79	1.70-1.80
4.	Free Amino Group	0.536	0.536	0.50-0.65ml of 1N NaOH/40ml of Haemaccel.
5.	Nitrogen	6.22	5.37	6.0-6.6 mgN/ml.
6.	Sodium	148	148	139-152 m.mol/l.
7.	Potassium	5.0	5.0	4.6-5.6 m.mol/l.
8.	Calcium	5.6	5.6	5.5-7.0 m.mol/l.
9.	Chloride	138	138	130-160 m.mol/l.

Perez Juan E and coworker reported that Furosemide is physically compatible with bicarbonate solution, heparin, insulin, morphine and nitroglycerin and incompatible with amiodarone, cisatracurium, haloperidol, midazolam and urapidil (Perez *et al.,* 2010).

Jasti and coworker also observed that Coadministration of furosemide with sodium bicarbonate, norepinephrine bitartrate, phenylephrine hydrochloride, calcium gluconate, procainamide hydrochloride, nitroglycerin, epinephrine hydrochloride, heparin sodium, vasopressin, and insulin, at the standardized concentration, was compatible (Jasti & Sara 2011).

Thompson and coworker reported that white precipitate formed when 1ml of solutions of esmolol hydrochloride

Table 5: Chemical compatibility of haemaccel with profenid drug's products: Haemaccel B. No.E015 and profenid 2 ml B. No. E005.

S. No.	Test	Result		Limit
		Before mixing of drug	After mixing of drug	
1.	Appearance	Clear, yellowish Solution	Clear, yellowish Solution	Clear, yellowish Solution
2.	pH	7.26	7.28	7.00-7.60
3.	Viscosity (Relative)	1.78	1.79	1.70-1.80
4.	Free Amino Group	0.556	0.578	0.50-0.65 ml of 1N NaOH/40 ml of Haemaccel.
5.	Nitrogen	6.43	6.55	6.0-6.6 mgN/ml.
6.	Sodium	148	148	139-152 m.mol/l.
7.	Potassium	5.1	5.1	4.6-5.6 m.mol/l.
8.	Calcium	5.5	5.6	5.5-7.0 m.mol/l.
9.	Chloride	145	148	130-160 m.mol/l.

10mg/ml in 5% dextrose injection and in 0.9% sodium chloride injection was mixed with 1ml of undiluted frusemide injection in a syringe and visually inspected at 0 and 15 minutes (Thompson & Thompson 1987).

Sofia and coworkers confirmed the stability of mixtures prepared with sodium furosemide (=120mg/day) and dexamethasone sodium phosphate (=40mg/day) for a period of 5 days and with independence of their storage at 4°C or 25°C (Sofia *et al.,* 2006).

Thalammer and coworker reported that furosemide (250 mg/50 ml) does not cause any incompatibilities or significant decrease of the antimicrobial drug concentrations of flucloxacin and ceftazidime (Thalhammer *et al.,* 2005).

Keyi and coworker found that famotidine is incompatible with furosemide (Keyi *et al.,* 1993). Lee and coworker studied on compatibility of cefoperazone sodium and furosemide in 5% dextrose. They found that both drugs retained at least 95% initial concentration for 5 days at 4°C, but for only 2 days at 25°C (Lee *et al.,* 1991).

Jeffrey and coworker reported that furosemide (1mg/mL) and Chlorothiazide (10mg/mL) are stable for up to 48 hours at room temperature in dextrose, either alone or in combination. Both of them also mixed with dextrose in a syringe can be used for infusion for a period up to 48 hours (Jeffrey *et al.,* 2010). Jim observed that Ciprofloxacin ready-to-infuse solution is incompatible with furosemide, heparin and teicoplanin (Jim 1993).

Thompson DF and coworker studied the compatibility of furosemide 4ml (40mg) with i.v. admixtures containing admixtures of amikacin 2 mg/ml, gentamicin 1.6mg/ml, kanamycin 2mg/ml, netilmicin 1.5mg/ml and tobramycin 1.6mg/ml, which were prepared in both 5% dextrose injection and 0.9% sodium chloride injection in minibags. Precipitates were formed in admixture containing gentamicin sulfate or netilmicin sulfate (Thompson *et al.,* 1985).

Valia and coworkers reported that Remifentanil is physically incompatible with furosemide but sufentanil is compatible with furosemide (Valia *et al.,* 2012).

This study also shows that not only ketoprofen but also haemaccel's parameters almost remain same before and after mixing. There are many studies have been reported regarding compatibility of ketoprofen with different drug products such as Nicolas Kambia and coworker reported that admixtures of the ready-to-use solution for injection of paracetamol and ketoprofen were physically compatible and chemically stable for up to 48 hours at room temperature (Nicolas *et al.,* 2006). Moselli and coworker reported that Ketoprofen in long-term continuous subcutaneous infusion (CSI) in combination with opioids (Morphine) is a feasible, safe, and effective in cancer pain (Moselli *et al.,* 2010).

David and coworkers studied compatibility and stability of ketoprofen with different drug products such as paracetamol, tramadole and nefopam over 24 hours at room temperature. They observed that there is no variation in concentration, pH and in visual inspection (David *et al.,* 2009).

Merighi and coworkers studied stability of cefodizime in five intravenous infusion fluids (0.9% sodium chloride, 5% dextrose in water, 10% dextrose in water, 5% amino acid injection, 3% polygeline) at room temperature and at 4 degrees C. Cefodizime concentrations remained greater than 90% of the initial concentrations in all infusion fluids for at least 24 hrs at room temperature and 6 days at 4 degrees C. They also studied compatibility of cefodizime with commonly used injectable drugs such as furosemide, ketoprofen etc in 0.9% sodium chloride and 5% dextrose at room temperature and found that concentrations remained greater than 90% of the initial concentrations of the solutions after mixture with all the tested drugs for at least 24 hours at room temperature (Merighi *et al.,* 1994).

Hamdi and coworkers reported that coadministration of binary mixtures of acetaminophen, nefopam, ketoprofen

and ketamine from the same bottle or infusion bag using the same venous line is feasible and stable at 25°C (Hamdi *et al.*, 2009).

Cruto and coworkers reported that ketoprofen in combination with morphine is a safe, feasible and effective in cancer pain (Cruto *et al.*, 2010).

In the same different studies have also been reported regarding compatibility of Prochlorperazine mesylate with different drug products for example Gardiner found that prochlorperazine mesylate is incompatible with Oxycodone injection but compatible with many drugs used in palliative care (Gardiner 2003).

Lober and coworker observed that Gallium nitrate is visually incompatible with prochlorperazine edisylate and other drug products as well at intervals up to 24 hours (Lober & Dollard 1993). Walker reported prochlorperazine is compatible and stable with hydromorphone over the whole 7 days period (Walker 1993).

Trissel and coworker observed visual incompatibility of amifostine with prochlorperazine by using a high-intensity light source, at 0, 1 and 4 hours after preparation (Trissel 1995). They also reported visual incompatibility of filgrastim with prochlorperazine, which were examined at 0, 1 and 4 hours after mixing (Trissel 1994). In the same ways Trissel observed visual incompatibility of fludarabine phosphate with prochlorperazine at a interval up to 4 hours (Trissel 1991).

Forman and coworker noted visual compatibility of midazolam with prochlorperazine after mixing, and then after 1, 2 and 4 hours (Forman 1987). Souney reported visual compatibility of cimetidine hydrochloride with prochlorperazine after 0.25, 1 and 4 hours (Souney 1984).

Takagi and coworker studied visual compatibility of foscarnet with prochlorperazine and examined visually at intervals of up to 24 hours. They observed delay precipitation and/or colour changes (Takagi & Lor 1990). But there are not any previous studies reported regarding compatibility of haemaccel with lasix, profenid and stemetil. Although these previous studies indicate that lasix, profenid and stemetil are compatible and incompatible with different drugs products which revealed that these drugs may be administered/co-administered with different drug's products safely and plasma substitutes as well.

This study also confirm that lasix, profenid and stemetil are chemically compatible with haemacel as previously reported study regarding compatibility and stability of haemaccel with different brands of cefotazime sodium (Mansoor & Nudrat 2009), also support this study because different brands of cefotaxime sodium also chemically compatible with haemaccel. Another study also reported that polygeline (Haemaccel) is suitable as a solvent for Cefotaxime Sodium for intraarterial treatment of infected ischemic lesions (Muller-Buhl & Diehm 1990), but unfortunately he did not test chemical parameters of compatibility. This study revealed that Haemaccel can be administered/co-administered with different drug's products safely, such as Lasix, Profenid and Stemetil. But it necessary or important to be investigated any drug's compatibility prior to co-administration with Haemaccel and continuing research must be conducted.

CONCLUSION

This study revealed that Haemaccel can be administered/co-administered with different drug's products safely. Other drug products should be studies in detail before it's co-administration with Haemaccel for safety, suitability, acceptability and efficacy and continuing research must be conducted.

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