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Biocompatibility Testing of Plastic Material (LDPE) of Plasma Substitutes (Polygeline)

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Abstract
The importance of plasma substitutes have been rising steadily. The main reason for its increasing use is handling with greater flexibility, therapeutic margin of safety, stability and compatibility, but their medical devices (containers) and their component materials may leach compound or have surface characteristics that may produce undesirable effects when used clinically. Due to least hazards of LDPE and most widely used plastic material in Plasma substitute biological reactivity tests of LDPE are performed to detect any unexpected and unacceptable leachable substance of plastic materials of bottles/containers which are stored at different temperature during study.In present studies biocompatibility testing of plastic material (LDPE) of two different plasma substitutes (polygelin) stored at different storage conditions at different time period did not show any eye irritation or eye injury or localized reaction in the test of eye irritation employed on rabbits. In the same way results of intracutanous test did not show erythema and edema on rabbit skin, which indicated that different plasma substitutes can be stored in LDPE containers at different temperature for their expiration time, shelf life or utility time restriction for hot and humid region of world for quality, safety, suitability, acceptability and efficacy.

Keyword: *Biocompatibility, polygeline, Low density polyethylene, Rabbit eye irritation test.*

Introduction
The importance and usage of plasma substitutes have been increasing due to its greater flexibility, safety and stability, but their primary container and infusion set may leach different type of compound or have surface characteristics that might produce undesirable side effects. There are many different factors that may be caused of leaching of substances from container during storage such as pH, temperature, time, surface treatment of plastic, containers configuration, type of polymers used, method of package preparation, light transmission and means of assembly or sterilization [1].The Pharmaceutical Manufacturers Association (PMA) recognized the need to develop standards for plastic materials as early as 1961[2, 3]. The FDA has given some limited direction concerning the evaluation and testing of polymeric materials. Current regulations, whether in accordance with the U.S. Food and Drug Administration (FDA), International Organization for standardization (ISO), or the Japanese Ministry of Health and Welfare (JMHW) require that manufacturers conduct adequate safety testing of their finished devices through pre-clinical and clinical phases as part of regulatory clearance process. Numerous/various testing methods are present in different pharmacopeia and guidelines of ISO, FDA and JMHW, to ensure the safety and biocompatibility of any plastic being used [4]. An increasing use of plastic container in plasma substitutes has led to an increasing number of adverse effects that may be as higher as 100,000 each year, from minor injuries to those very serious causing deaths [5]. Several studies have shown the leaching of di-(2-ethylhexyl) phthalate (DEHP) from PVC bags [6,7]. DEHP is the predominant

plasticizer used to make the bags soft and pliable. This plasticizer is known to be responsible for change in structure and function of liver in animals, reduction body weight and liver weight in adult male rats [8,9]. Non-PVC bags for example multilayer containers do not contain plasticizers and are recommended by manufacturers for admixture of total nutrient solution, containing lipophilic constituents, used for delivering total parenteral nutrition. The other main problem is the possible adsorption of drugs on the inner plastic surface of container [10,11]. Oral solutions, sterile solutions in small volume container systems, and sterile solutions in large volume parenteral container/closure system should be tested at both long term and accelerated conditions to ensure that no adverse effect is produced from any interactions[12]. For this reason present study is carried out to check chemical hazards, relate to compatibility between the drug products and containers and any "exchange" that may occur from drug products to containers or containers to drug products, these may involve various chemical interaction or simple migration/leaching, to determine the biological response of animals to plastic materials because of their current and future application, their interaction with drug products or patients, for quality, safety and stability purposes.

Experimental design and methods

Haemaccel batch No. D070 kept at room temperature (Average 28°C & 45% ± 2 relative humidity) for 3 years and at 40 °C (Average 40°C & 75% relative humidity) in a climatic chamber for 6 months, in the same ways Gelofusine batch No. 4212E41 also kept at room temperature (Average 28°C & 45% ± 2 relative humidity) for 3 years and 30 months at 40 °C (Average 40°C & 75% relative humidity) in a climatic chamber. After required time periods plastic materials of Haemaccel and Gelofusine's bottles were evaluated/check for ocular irritation (Topical) test on rabbits and Haemaccel also evaluated for intracutaneous test on rabbits at room temperature (Average 28°C & 45% ± 2 relative humidity) for 3 years, at 40 °C (Average 40°C & 75% relative humidity) in a climatic chamber for 6 months and 3 months in sun light.

Ocular irritation test

Selected three healthy, albino rabbits having no visible eye irritation and not previously used for eye irritation test. Prepared normal saline and added a sample of plastic having thickness, < 0.5 mm to 1 mm and subdivided into strips of about 5 x 0.3 cm and remove particulate matters by washing with water for injection. Then placed a plastic sample in an extraction container and add 500 ml of normal saline and extracted by heating in an autoclave at 121 ºC for 60 minutes and cool sample at room temperature.

Shake for several minutes and decant it, into a dry sterile vessel. Store it at a temperature between 20 and 30 ºC. Blank also prepared for parallel injections and comparison.

Before instillation of blank and sample, examine both eyes of rabbits which must be free from any eye defects. Restrained all rabbits firmly and gently until quiet. Gently pulled lower lid away from eyeball to form a cup and instilled about 200 µL of blank in one eye and hold the lid together for about 30 seconds and 200 µL of sample extract into other eye of rabbit. After instillation of blank and sample extracts examined both eyes of rabbit at 24, 48 and 72 hours intervals. The requirements of test are met if sample extract show no significant irritation over blank extract during observation period [13].

Intracutaneous Test

This test is designed to determined/evaluate irritant effect of toxic leachable present in extracts of test materials following intracutaneous injection into rabbits. Select healthy rabbits that were free from mechanical irritation or trauma.

Agitated extract and closely clipped the fur on rabbit's back on both sides of spinal column over a sufficiently large area. Removed loose hair by means of vacuum and swab skin of rabbit with diluted alcohol and dry skin prior to injection. For each sample use two rabbits and injected each intracutaneously, using one side of rabbit for sample and other side for blank.

Examined and observed injection sites for evidence of any tissue reaction for example erythema, edema and necrosis. Swab skin lightly with dilute alcohol to facilitate reading of injection sites. Observed the rabbits at 24, 48 and 72 hours after injection. Rate observations on a numerical scale for extract of sample and for blank. The average erythema and edema scores for sample and blank sites are determined at every scoring interval (24, 48 and 72 hours) for each rabbits. After 72 hours scoring all erythema scores plus edema scores are totaled separately for each sample and blank. Divide each of totals by 12 (2 rabbits x 3 scoring periods x 2 scoring

categories) to determine overall mean score for each sample versus each corresponding blank. The requirements of tests are met if difference between sample and blank mean score is 1 or less. If at any observation period average reaction to sample is greater than average reaction to blank, repeat test using three rabbits [14].

Results

The results of observation on two different plasma substitutes i.e., Haemaccel batch No. D070 and Gelofusine batch No. 4212E41 at different storage condition and at different time periods do not show any acute irritation or eye injury after instillation of extracts of plastic material of bottles. 200 microlitres extract of bottles of plasma substitutes was instilled in eye of rabbits and examined the eyes at 24, 48 and 72 hours intervals, according to the method, that did not show any changes in the eyes of rabbits i.e., any injury on conjunctive, cornea, iris and flushed eye of all three rabbits. Results are presented on table 1 and 2. No change was observed in appearance and shape of bottles of plasma substitutes after storage at different temperature and different storage condition.

In the same way results of intracutanous test did not show erythema and edema on rabbit skin after storage at different time periods and different storage condition. As shown in table 3.

Amount and Injection Sites

S/No.	Extract or blank	Number of sites (per rabbits)	Dose, micro litre per site
1	sample	5	200
2	blank	5	200

Table. 1 Biological Reactivity Test of Haemaccel Bottlec(Eye Irritation Test)

S/No	Batch No	Storage Condition	Storage Time	Appearance of Bottles	Flushed eye	Conjunctive	Cornea	Iris
1	D070	Room temperature	0 month	Satisfactory	No	No	No	No
2	D070	Room temperature	3 years	Satisfactory	No	No	No	No
3	D070	At 40 ºC	6 months	Satisfactory	No	No	No	No

Table. 2 Biological Reactivity Test of Gelofusine Bottle (Eye Irritation Test)

S/No	Batch No	Storage Condition	Storage Time	Appearance of Bottles	Flushed eye	Conjunctive	Cornea	Iris
1	4212E41	Room temperature	0 month	Satisfactory	No	No	No	No
2	4212E41	Room temperature	3 years	Satisfactory	No	No	No	No
3	4212E41	At 40 ºC	30 months	Satisfactory	No	No	No	No

Table.3 Evaluation of skin reaction of Haemaccel bottles at different storage condition.

S/No	Batch No	Storage Condition	Storage Time	Appearance of Bottles	Erythema And Eschar Formation	Edema Formation
1	D070	Room temperature	0 month	Satisfactory	No	No
2	D070	Room temperature	3 years	Satisfactory	No	No
3	D070	At 40 ºC	6 months	Satisfactory	No	No
4	D070	sun light	3 months in sun light	Satisfactory	No	No

Discussion.

Packing is an important component in the fate of drug in a dosage form. Improper packaging and improper storage of drug products may or will cause larger than expected losses in purity, strength and quality of drug products. Therefore, packaging material must be inert in relation to its content. It should neither release nor absorb substances.

With the proliferation of new polymers and new polymer process technology, most of the less desirable characteristics of plastic containers have been overcome [4].

Due to their insolubility in water and relative chemical inertness, pure plastics generally have

low toxicity in their finished state. However, plastics often contain a variety of toxic additives. For example, plasticizers like adipates and phthalates , catalyst like chromium oxide, pigment such as lead chromate which may cause undesirable effects. Many substances that are known endocrine disrupters are used as additions to plastic and that they leach out from them, such as Di (2-ethylhexyl) phthalate [15], that is used 95% as a plasticizer in production of polyvinyl chloride and vinyl chloride resin. Polyvinyl chloride (PVC) materials for infusion bags are commonly used for the administration of infusion drug admixtures because they offer several advantages over conventional glass containers, but several studies found that DEHP leached from PVC blood bags, IV bags and tubing into blood, blood products, and medical solutions. DEHP has been measured in blood products (whole blood, plasma, platelet, and red cell concentrates) in concentrations ranging from 4 to 650 mg/liter. DEHP has been measured in concentrations ranging from 3.1 to 237 mg/liter in solutions containing drugs and solvents and 5 mg/liter in sterile water and salt and sugar-based solutions. For example Kambia and coworker (2005) studied the stability and compatibility of three drugs, nitroglycerin, diazepam and chlorpromazine with a new multilayer infusion bag and PVC, their study confirms that these three drugs are incompatible with PVC bags so these three drugs would not be stored in PVC bags, on contrary in new multilayer bags, no loss of drug observed [16]. Gotardo and Monteiro (2005) also reported the migration of DEHP from PVC bags into 0.9% sodium chloride containing cyclosparine at 12 hours of contact [17]. Faouzi and coworkers (1999) determined stability of quinine (quiniforme and quinimax) in polyvinyl chloride (PVC) containers, and release of diethyhexyl phthalate (DEHP) from PVC bags into intravenous infusions of quinine was also measured. They reported that quiniforme (500 mg/ 500 ml) and quinimax (400 mg in either 250 or 500 ml) in a 5% dextrose solution are compatible with the Macoflex (PVC) bags when stored for 8 h at room temperature and ambient light for 48 or 72 h at 4°C, or for a 4-day period at 45°C without protection from light. However, a significant release of DEHP reaching up to 21µg/ ml was observed when quiniforme and quinimax were associated with other drugs during a 4-day storage period at 45°C [18]. Moulay and coworker (1995) determined stability of miconazole in polyvinyl chloride (PVC) containers and measured the release of diethylhexyl phthalate (DEHP) from PVC bags into intravenous infusions of miconazole over 24 hours storage at 2–6°C and 22–26°C, no loss of drug observed but they recommended that to minimize patient exposure to DEHP, miconazole solutions should be infused immediately after their preparation in PVC bags [19]. Arcy (1983) pointed out that some drugs bind on plastic (PVC) and other surfaces. For examples insulin, glyceryl trinitrate, diazepam, chlormethiazole, vitamin A acetate and vitamin A palmitate, isosorbide dinitrate, phenothiazine, hydralazine hydrochloride, thiopentone sodium,warfarine sodium[20].

Several studies have also been reported the leaching/migration of antimony and brominated compouns from plastic bottles like Cheng and coworker (2010) reported that heating and microwaving enhance antimony leaching significantly in PET plastic bottles [21]. Andra and coworker (2011) reported co-leaching of antimony and brominated compounds from drinking water bottles [22]. Shotyk et al, (2006) reported contamination of Canadian and European drinking water bottles with antimony from PET containers [23]. Keresztes et al, (2009) also found leaching of antimony from polyethylene terephthalate (PET) bottles into mineral water [24]. But others scientists reported opposite finding of their studies such as Laurence et al, (2004) reported that sufentanil citrate 500 µg with levobupivacaine hydrochloride 625 mg) in 0.9% sodium chloride injection 500 ml in PVC infusion bags may be prepared in advance and stored for 58 days at 4 °C without major changes affecting concentration[25]. Gerar and coworker (1993) studied stability and the compatibility of 5-Fluorouracil (5-FU) and d, l-folinic acid (FA) in combination in intravenous admixtures in PVC container. They reported that both drugs did not show significant fixation of FA or 5-FU on the PVC bags during 120 hours [26]. Dine et al, (1991) reported that no significant loss of vinblastine, vincristine and vindesine observed during storage 7 days at 4°C with protection from light in parenteral solutions (5% glucose or 0.9% NaCl) using PVC bags [27]. Khalfi et al, (1996) reported the stability and compatibility of vancomycin hydrochloride injection in various diluents with polyvinyl chloride (PVC)

containers under different conditions of temperature and light. They observed no visual change, no color change, no visible precipitation and no loss of vancomycin hydrochloride 5 mg/ml, and it was compatible and stable with PVC bags for at least 48 h at 22°C without protection from light and for at least 7 days at 4°C with protection from light [28]. Faouzi et al, (1993) studied the Stability and compatibility of pefloxacin, ofloxacin and ciprofloxacin with PVC infusion bags at room temperature without protection from light.They found satisfactory results of pefloxacin and ciprofloxacin during 6 h of storage, irrespective of the infusion solution (5% glucose or 0.9% NaCl) but significant variations with ofloxacin in the solution of 5% glucose, but remaining below 10% [29]. Fischer et al,(1997) studied the stability of fosphenytoin sodium with intravenous solutions in glass bottles, polyvinyl chloride bags, and polypropylene syringes. They concluded that Fosphenytoin sodium, either undiluted in polypropylene syringes or diluted with NaCl 0.9% or dextrose 5% (D5W) in PVC bags, remains stable for at least 30 days at room temperature, under refrigeration, or frozen. After removal from the freezer, fosphenytoin can be thawed, kept at 4 or 25 degrees C for 7 days, and then returned to the freezer for another 7 days. Admixtures of fosphenytoin sodium in various other intravenous fluids are stable for at least 7 days at room temperature [30].

Faouzi et al,(1994) determined the stability of teniposide in various diluents with polyvinyl chloride (PVC) bags and measure leaching of DEHP from PVC bags. They found no significant drug loss, but they recommended that teniposide solution may be stored in a glass or polyolefin containers [31].

In the present study low density polyethylene is used against biological reactivity test, which is ranked as least hazardous polymer and most widely used food-wrapping material. Which constitute 46% of the European virgin plastic production. Food-wrap grades contain antioxidants to minimize degradation during processing and, in the final films, such additives are normally present at levels of several hundred ppm. During use, the antioxidants may migrate into food stored in LDPE wraps. Therefore, EP (European pharmacopoeia) refers to grades of LDPE which are free from antioxidants, although, it consists of pure polymer [12]. On the other hand, preliminary studies indicate that LDPE too, may cause problems. Some studies have found that LDPE-based wrap leaches measurable levels of chemicals such as BHT, Chimassorb 81, Irganox PS 800, Irganix 1076, and Irganox 1010 into vegetable oil, because they may contain residues from the process of polymerization, additives, processing aids, or master batch constituents, which can be critical for large and small volume parenterals [16]. Over time, almost all plastic degrades, especially when exposed to heat, and this means it can start leaching its chemical components. Again, LDPE-based products do far better than DEHA products when tested for leaching, but they aren't fail-proof [32].

Schwape and coworker (1987) studied migration of BHT and Irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids. They found that BHT, a much smaller and more volatile molecule than Irganox 1010, migrates more rapidly into foods, but the differences are less for FSL [33]. But on other hand Beitz et al, (1999) studied adsorption effect of LDPE with antineoplastic drugs. They found that antineoplastic drugs are stable in glass bottles, LDPE containers and PVC bags, the best stability in glass bottles followed by LDPE containers and PVC bags [34]. Sautou-Miranda et al, (1999) studied the compatibility of Paclitaxel with low-density polyethylene containers (ECOFLAC) under different temperature and light conditions. They concluded that Paclitaxel at 0.4 and 1.2 mg/ml in 5% glucose is physically and chemically stable in ECOFLAC® for 5 days in ambient light and in the dark, at ambient temperature and in a refrigerator at +4°C. No DEHP is released from the ECOFLAC® containers into the Paclitaxel solutions. The stability of Paclitaxel in ECOFLAC® is comparable to that obtained in glass containers [35]. Different scientists also confirmed that Paclitaxel is compatible with glass or polypropylene bottles, and polyolefin bags [36, 37, 38, 39].

This study also confirmed after studied of eye irritation and intracutanous test against LDPE of plasma substitutes, that LDPE is safe plastic for storage of different plasma substitutes. As it is the major commercial polymers polyethylene which are extremely resistant to biodegradatio, i.e., degradation by micro-organisms. According to Andrady (1998) only 0.1% of the carbon in a polyethylene polymer will be transformed into

CO_2 per year by biodegradation, even under optimal laboratory exposure conditions [40], it is also durable and biochemically inert due to its large molecular size, and is therefore not regarded as hazardous for human health or the environment. However, if polymerisation reactions are rarely complete and, therefore, also unreacted residual monomers can be found in the polymeric material, several of which are hazardous for human health and the environment and/or affects polymer properties. The loss of certain preservatives by absorption or adsorption , particularly with LDPE, is generally well recorded, like, phenol, chlorbutol, 2 phenyl ethanol are absorbed and thiomersal can be adsorbed [12].

All of these observations and results are useful for storage of these plasma substitutes at different temperature for their expiration time, shelf life or utility time restriction for hot and humid region of world.

CONCLUSION

This study revealed that Haemaccel and Gelofusine are suitable for storage at different temperature and at different storage conditions until its expiry date, shelf life or utility time in LDPE containers. For their quality, safety, suitability, acceptability and efficacy.

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