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IMPROVED RED CELL STORAGE IN DI (ISONONYL) CYCLOHEXANE 1, 2-DICARBOXYLATE (DINCH) AND DI 2 ETHYL HEXYL TERE PHTHALATE (DEHT) PLASTICISED PVC BLOOD BAGS

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ABSTRACT

DEHP plasticized PVC is the preferred material for making bags for the storage of blood and blood components such as whole blood, red cells, platelets and plasma. Various studies are in progress to find alternatives for DEHP. This paper presents our studies on the use of plasticisers,di-2-ethyl hexyl terephthalate (DEHT) manufactured by M/s Eastman, U.S.A and di(isononyl)cyclohexane 1,2-dicarboxylate (DINCH) manufactured by M/s BASF, Germany, for making blood bags for the storage of RBCs. The present study is a comparative assessment of the suitability of DEHT and DINCH plasticised PVC bags for the storage of RBCs in the presence of preservative solutions AS3 and AS5. RBCs could be stored in DEHT and DINCH plasticised PVC bags for only up to 35 days in the presence of RBC preservative solution AS 5. Above this period, the hemolysis of RBCs was higher than the prescribed limit and cell swelling was higher. When RBCs were stored in 100ml AS 3 and increased volume of 125ml AS 5, the hemolysis was significantly lower and within the limits. Mean cell volume (MCV) was maintained better. Other parameters such as RBC count, Hb, Hematocrit, p H , PCO2, HCO3, Lactate, Na+, K+, Glucose etc showed comparable results. The present studies show that RBCs could be stored in DEHT and DINCH plasticised PVC bags for up to 42 days maintaining the accepted limits of hemolysis and other quality parameters using 125ml AS 5 and 100ml AS 3 additive solutions.

KEY WORDS: **Red blood cell (RBC), Non DEHP plasticizer, DINCH plasticizer, DEHT plasticizer, RBC storage.**

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INTRODUCTION

DEHP plasticized PVC is widely used for making storage bags for blood and blood components such as whole blood, red cells, platelets and plasma. The plasticiser DEHP has a remarkably beneficial effect to reinforce RBC membranes and thereby to prolong the storage life of red cells by reducing lysis. DEHP is not covalently bonded to PVC, it can be leached out of PVC with time. Various studies are in progress to find alternatives for DEHP[1-8].

Other plasticisers for blood bag manufacture.

Non phthalate plasticizers such as Tnioctyltrimellitate (TOTM), Butyryl-n-tri hexylcitrate (BTHC), Di- n-decyl phthalate (DnDP) have been in use for certain special applications for blood storage bags such as for making platelet storage and pooled platelet storage bags. TOTM plasticizer is suitable for making platelet storage bags. RBCs could be stored in these bags for only up to 21 days [9]. BTHC plasticised PVC bags has been shown suitable for making platelet storage as well as RBC storage bags[10]. DnDP plasticized PVC is suitable for platelet preservation for up to 5 days[11]. Blood bags made of special poly olefins have been found to be suitable for the storage of platelets[12].

DEHT (Di-2ethyl hexyl terephthalate)

The Eastman Chemical Company offers this plasticizer which is reported to be a suitable replacement for DEHP[13,14]. This plasticizer has been extensively tested for human and ecological toxicity, genotoxicity and developmental and reproductive toxicity[15,16]. The results show that this compound is essentially non toxic, non carcinogenic, mutagenic or teratogenic.

HEXAMOLL - DINCH (Diisononyl Cyclohexane Dicarboxylate)

This is an innovative plasticizer introduced by M/s. BASF for sensitive applications under the name DINCH. It has a proven excellent toxicological profile, no carcinogenicity, and low migrating characteristics [17,18].

Storage of RBC in DINCH plasticised PVC bags.

Recent studies report that 42 day RBC preservation is possible in DINCH plasticized PVC bags using additive solutions such as Optisol, PAGGSM, PAGGSS, E Sol 5, Sol X and AS3 solution[19-24].The various studies reported in this regard are the following:

- 42 day Storage of RBC in DINCH PVC bags using additive solution Optisol (AS 5) 100 ml with weekly shaking, (BASF, 2011).
- 42 day Storage of RBC in DINCH PVC bags using red cell additive solutions such as PAGGSM, E sol 5 and Solx (Sanquin Research, Netherlands and Fenwal).
- 42 day Storage of RBC in DINCH PVC bags using red cell additive solution AS3 (Sanquin Research, Netherlands).

Present study

The studies reported here investigate the suitability and performance of DEHT, Di-2-ethylhexyl terephthalate compared to DINCH (Diisononyl Cyclohexane Dicarboxylate ester) plasticised PVC bags for the storage of red blood cells in the presence of AS 5 and AS 3 additive solutions.

MATERIALS AND METHODS

Blood bags used for the study

The blood bags used for the study were as follows:
Collection bags: Quadruple bag system 450ml consisting of main bag, a transfer bag containing red cell additive solution, platelet storage bag and transfer bag (All bags were of capacity 450ml). This was made of sheets (A) DEHTplasticised PVC (B) DINCH plasticised PVC and (C) DEHP plasticised PVC. These bags were made at Terumo Penpol Ltd, India.

Characteristics of test bags

The characteristics of the materials of the test bags are given in Table 1. The bags were tested for physical, chemical and toxicological requirements for conformance with the ISO 3826 standard for blood bags and ISO 10993 standard for medical devices.

Leucocyte reduction filters

The leucocyte reduction filters used in the study for RBC filtration were Asahi Sepacell CRC RX 01.

Compositions of the anticoagulants used.

The compositions of the red cell additive solutions used in the study are given in Table 2.

Blood collection and component separation

Blood from the test donors was collected in primary bag of QB 450 ml bag containing CPD (citric acid-phosphate-dextrose) anticoagulant solution. After allowing the bags to stand for two hours at 20 – 22°C, the bags were centrifuged at 3600 rpm for 10 minutes at 20°C using Cryofuge 5500 i.

CRC (Concentrated Red Cell) preparation:

The top platelet poor plasma (PPP) was transferred to the plasma storage bag and buffy coat was transferred to the transfer bag. The CRC was retained in the primary bag to which the red cell preservative solution was added from storage solution bag. The mix was filtered through the leucocyte reduction filter in to the test bag, sealed and stored at 4-6^{0}C. RBC samples were drawn on 0, 21, 28, 35 & 42 day of storage for testing and analysis.

Parameters studied

1. RBC count, WBC count, Plt. Count, HCT, MCV and Total Haemoglobin were measured using Sysmex cell counter XP-100.
2. pH, pO2, pCO2, HCO3, K+, Na+ , Lactate and glucose were measured using Blood gas analyser ABL 800 Radiometer.
3. Hemolysis was determined as percentage of total Hb after correction for Hct using the equation.

$$\% \text{ Hemolysis} = \frac{(100 - \text{Hct}) \times \text{Plasma Hb (g/dl)}}{\text{Total Hb (g/dl)}}$$

RESULTS AND DISCUSSION

The in-vitro storage characteristics of RBCs stored in DEHT and DINCH bags in the presence of additive solutions (a) 100ml AS 5 (b) 125ml AS 5 and (c) 100ml AS 3 are given in Tables 4-6. The characteristics of RBCs stored in a DEHP plasticised PVC in the presence of 100ml AS 5 is given in table 3 for comparison. Eight blood studies were carried out for each category.

DINCH plasticised bags

Comparable results were obtained on storage using the three additive solutions studied for all parameters except hemolysis and MCV.

Hematological studies

RBC count, Hematocrit and Hb

The deviation observed was less than 5% after 42 day storage.

Mean cell volume (MCV)

MCV which is indicative of cell swelling was low in the presence of 125ml AS 5 and 100ml AS 3 than when 100 ml AS 5 was used.

Biochemical studies

pH, pO2 and pCO2

p H was maintained above 6.3 to the end of the storage period in all cases. The p O2 showed a gradual increase up to 42 days in the bags tested. p CO2 showed a steady increase up to 28th day of storage, after which get reduced.

HCO3

The reduction of HCO3 is due to the lactic acid generated by glycolysis.

Plasma Na+, Lactate

Plasma Na+ showed a gradual decrease. Lactate showed a gradually increasing pattern for all the samples.

Hemolysis

RBCs had consistently higher hemolysis when stored with 100ml AS 5. After 42 days storage 50% RBCs (4 out of 8 samples) under study exceeded 0.8% hemolysis. In the presence of 125ml AS 5and 100ml AS 3, the hemolysis was significantly lower and was within the limit of 0.8%. (Figure 1& Tables 4-6).

The results indicate good storage conditions for RBC in DINCH bags with 125 ml AS 5 and 100ml AS 3 solutions up to 42 days. The performance for RBC in DINCH bags with 100ml AS 3 solution was found to be similar to that of RBC in DEHP plasticised PVC with 100ml AS 5 solution.

DEHT plasticised bags

The results obtained for DEHT plasticised bags were similar to that obtained for DINCH bags.

Hematological studies

RBC count, Hematocrit and Hb

The deviation observed was less than 5% after 42 day storage.

Mean cell volume (MCV)

MCV which is a measure of cell swelling was maintained better with 125ml AS 5 and 100ml AS 3 than when 100ml AS 5 was used.

Biochemical studies

pH, pO2 and pCO2

p H was maintained above 6.3 to the end of the storage period in all cases. The p O2 showed a gradual increase up to 42 days in the bags tested. p CO2 showed a steady increase up to 35th day of storage, after which get reduced.

HCO3

The HCO3 showed a gradual reduction during the storage period due to the lactic acid generated by glycolysis.

Plasma Na+, Lactate

Plasma Na+ showed a gradual decrease. Lactate showed a gradually increasing pattern for all the samples.

Hemolysis

RBCs had consistently higher hemolysis when stored with AS 5 100ml. After 42 days storage 80% RBCs (7 out of 8 samples) under study exceeded 0.8% hemolysis. In the presence of 125ml AS 5 and 100ml AS 3, the hemolysis was significantly lower and was within the limit 0.8% (Figure 2 & Tables 4-6).

Table 1
Characteristics of PVC sheets used for making bags in this study

Property	DEHT PVC A	DINCH PVC B	DEHP PVC C
Average thickness (+/- 0.02mm)	0.39	0.39	0.39
Hardness Shore A ASTM D 2240	82	79	80
Tensile Strength (MPa) ASTM D882	22.6	20.11	23.53
Elongation at break(%) ASTM D882	372	355	390

Table 2
Compositions of the additive solutions

AS 5 100ml	**0.877g NaCl 0.525g Mannitol 0.9 g Glucose monohydrate 0.030g Adenine**
AS 5 125ml	1.096g NaCl 0.656g Mannitol 1.125g Glucose monohydrate 0.0375g Adenine
AS3 100ml	0.41g NaCl 1.1g Glucose monohydrate 0.588g Sodium citrate 0.276g Sodium phosphate 0.042g Citric acid 0.03g Adenine

Table 3
Storage of CRC in DEHP PVC bags using 100ml AS 5 solution (n= 5)

	Day 0	Day 21	Day 28	Day 35	Day 42
Sample			DEHP		
pH	6.93±0.03	6.54±0.02	6.48±0.02	6.43±0.03	6.39±0.03
pCO2(mm Hg)	67.84±7.89	123.64±11	102.56±8.38	101.6±9.33	92.41±6.53
pO2(mm Hg)	40.59±9.08	76.87±23.07	103.24±44.52	113.31±40.78	124.54±39.05
HCO3(mmol/L)	12.6±0.49	9.79±1.51	7.23±0.75	6.4±0.61	5.3±0.66
K+(mmol/L)	2±0.46	32.64±3.75	33.14±5.19	41.06±2.77	45.6±4.08
Na+(mmol/L)	136.57±1.51	108.57±5	104.71±3.74	100±4.12	98.29±3.15
LAC(mmol/L)	4.84±0.62	19.99±1.59	22.77±1.35	25.53±1.46	28.61±1.13
Glu(mmmol)	436.25±17.2	394.75±25.5	363.25±21	318.8±16	319.25±22
RBC(X10<6/µl)	6.43±0.26	7.03±0.44	6.76±0.31	6.53±0.36	6.38±0.13
Hct%	55.41±2.03	57.23±5.18	59.13±3.33	58.81±3.84	57.69±2.3
MCV (fL)	86.1±3.1	88±3	87.75±3.22	88.85±3.3	88.75±2.9
lysis%	0.06±0.01	0.1±0.03	0.16±0.02	0.25±0.01	0.32±0.01

Table 4

Storage of CRC in DEHT and DINCH PVC bags using 100ml AS 5 solution (n= 8)

	Day 0		Day 21		Day 28		Day 35		Day 42	
Sample	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH
pH	7±0.02	6.99±0.03	6.69±0.03	6.7±0.04	6.58±0.04	6.6±0.04	6.55±0.04	6.5±0.05	6.52±0.04	6.5±0.05
pCO2(mm Hg)	76.7±5.2	78.26±5.34	112.8±4.7	107±6.14	109.8±3	98±7.3	106.18±6	96±4.6	99.48±7	86.5±5.7
pO2(mm Hg)	24.3±8	26.85±5.07	53.6±10.1	57±7.5	68.8±14	80±17.17	82.8±22.2	111±41	110.2±39.3	157±62
HCO3(mmol/L)	18.15±0.66	17.91±0.82	13±1.22	13±0.73	9.8±1.01	9.1±0.68	8.8±1.03	8±0.66	7.71±1.09	6.95±0.72
Na+(mmol/L)	140.3±1.36	140±1	116±2.4	114±3.3	116±2.4	109±4	108±3.14	106±3.8	104±3.31	103±3.4
LAC(mmol/L)	4±0.42	3.26±0.4	9.2±2.2	6.6±1.4	19.68±2.3	20±2.4	23±1.9	24±1.7	24.2±2.1	25.3±1.7
RBC(X10<6/µl)	5.4±0.27	5.63±0.3	5.7±0.3	5.6±0.2	5.2±1.49	5.8±0.2	5.8±0.3	5.8±0.3	5.8±0.3	5.85±0.23
Hct%	50.55±1.3	49.7±4.72	49.5±2.9	50±3.8	50.9±2.1	52±14	51.5±2.2	52±4	51.8±2.3	52±4.3
MCV (fL)	84.56±2.5	84±4.3	86.55±3.05	87.6±3.5	87.6±3.6	87±3	88.3±3.31	89.8±3.7	88.8±3.4	89.4±3.93
lysis%	0.02±0.01	0.028±0.01	0.176±0.02	0.17±0.025	0.44±0.03	0.38±0.06	0.54±0.04	0.52±0.06	0.89±0.08	0.7±0.13

Table 5

Storage of CRC in DEHT and DINCH PVC bags using 100ml AS 3 solution (n= 8)

	Day 0		Day 21		Day 28		Day 35		Day 42	
Sample	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH
pH	6.8±0.01	6.8±0.036	6.5±0.04	6.56±0.02	6.4±0.05	6.5±0.14	6.44±0.05	6.46±0.02	6.4±0.05	6.43±0.02
pCO2(mm Hg)	62±3.93	55.27±13.42	75.36±4.6	53.97±6.8	73.08±8	53.75±7.28	84.46±7.7	48.02±8.16	64.9±7.6	45.37±3.33
pO2(mm Hg)	38.6±2.24	42.15±7.4	76.24±13	120.5±36.1	136.4±47	185.75±36.5	92±21	238.2±3.41	184±36	251±5.26
HCO3(mmol/L)	11.12±0.52	11.72±0.81	6.68±0.7	6.6±0.24	4±0.5	5.67±0.27	5±0.45	4.97±0.04	3.2±0.5	3.97±0.31
K+(mmol/L)	2±0.09	1.85±0.47	19±6.3	16.65±1.9	27.8±3.8	20.9±1.4	25.4±3.8	23.65±0.85	30±3.4	24.95±1.42
Na+(mmol/L)	137±0.5	138.25±1.15	105±6.8	113.75±2.4	101±6	113±3	104±6.5	110±3.19	92.4±5.3	103±3.44
LAC(mmol/L)	3±0.16	3.12±.31	16.3±1.75	13.6±0.9	14.3±0.7	14.45±.99	16±1.2	14.07±0.66	27±3.2	20.5±1.6
Glu(mmmol)	456±10	486±10	425±39	475±28	355±45	456±30	391±42	518±39	312±45	418±28
RBC(X10<6/µl)	7±0.4	6.07±0.32	7±0.4	6.12±0.32	6.8±0.35	6.13±0.32	6.8±0.4	6.08±0.34	6.85±0.34	6.18±0.33
Hct%	58±1.2	51.35±2.66	58±1.3	51.35±2.66	58±1.7	51.7±2.5	57.4±1.7	51.3±2.5	58±0.85	52.27±2.8
MCV (fL)	83.2±3.6	84.67±3.78	84±3.4	85.2±4	85±3.7	84.4±4.2	84±3.5	84.2±4.5	84.7±3.8	84.65±4.74
lysis%	0.076±0.02	0.08±0.06	0.34±0.06	0.26±0.07	0.45±0.024	0.25±0.09	0.37±0.04	0.29±.07	0.5±0.045	0.3±.06

Table 6

Storage of CRC in DEHT and DINCH PVC bags using 125ml AS 5 solution (n= 8)

	Day 0		Day 21		Day 28		Day 35		Day 42	
Sample	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH	DEHT	DINCH
pH	7±0.04	6.99±0.03	6.58±0.04	6.59±0.03	6.46±0.05	6.51±0.04	6.42±0.03	6.46±0.04	6.39±0.04	6.44±0.05
pCO2(mm Hg)	47.53±7.64	48.38±5.06	64.87±7.9	73.43±9.3	98.16±12.25	75.53±5.71	99.78±12.7	70.5±4.53	91.13±12	64.2±4.83
pO2(mm Hg)	38.93±11.49	36.51±0.03	73.21±21.65	93.32±28.9	74.87±26.1	150.83±63.9	85.88±44.4	212.8±45.8	121.5±55.4	222.75±25.3
HCO3(mmol/L)	9.27±0.64	9.7±0.44	5.77±0.79	6.7±0.91	6.75±0.93	5.77±0.6	6.11±0.4	4.76±0.6	5.25±0.7	4.1±0.55
K+(mmol/L)	1.68±0.42	1.42±0.13	20.55±2.34	18.3±0.95	23.07±2.3	22.85±1.75	24.8±2.4	25.48±1.41	28.75±3.7	27±2.24
Na+(mmol/L)	138.25±1.65	138.12±1.02	112.75±3.81	115.12±2.5	109±44.5	111.25±2.84	105.83±5.2	106±28.6	96.25±4.7	98.12±3.04
LAC(mmol/L)	3.95±0.89	3.7±1	17.12±1.31	16.87±1.7	15.31±1	16.02±1.29	13.21±0.37	13.8±0.55	25±1.8	25.25±2.93
Glu(mmmol)	-	436.25±8.6	373±37	394.75±27	343±42	363.25±31	310±39	318.8±31	309±51	319.25±42
RBC(X10<6/µl)	6.79±0.53	6.57±0.14	6.85±0.56	6.52±0.12	6.68±0.42	6.48±0.16	6.84±0.55	6.53±0.19	6.72±0.5	6.52±0.22
Hct%	55.72±3.06	56.07±1.7	51.34±20.3	56.76±1.9	57.26±3	56.28±2	57.69±3	56.61±1.9	57±4	56.74±1.8
MCV (fL)	84.91±5.3	85.28±3	85.28±6.29	86.69±2.9	85.86±6.5	86.61±3.3	86.03±6.5	86.86±3.45	86.55±6.6	87.11±3.84
lysis%	0.09±0.06	0.05±0.01	0.25±0.13	0.18±0.07	0.37±0.1	0.29±0.08	0.4±0.1	0.38±0.1	0.5±0.1	0.45±0.1

Figure 1

DINCH PVC bags - Hemolysis(%) of RBCs in various anticoagulant solutions

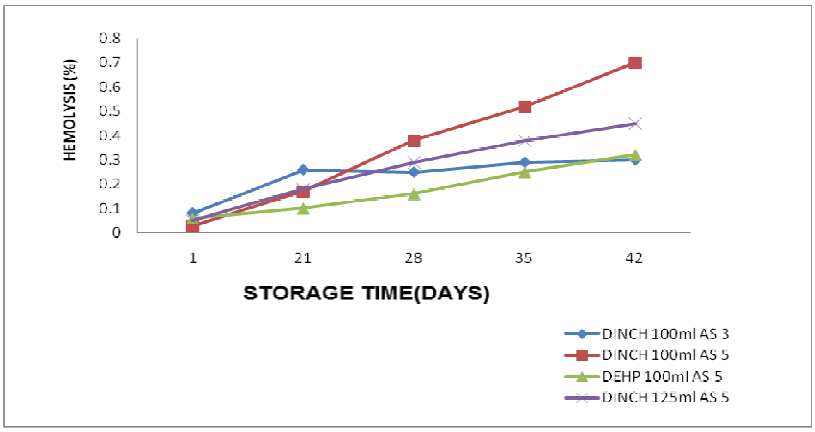
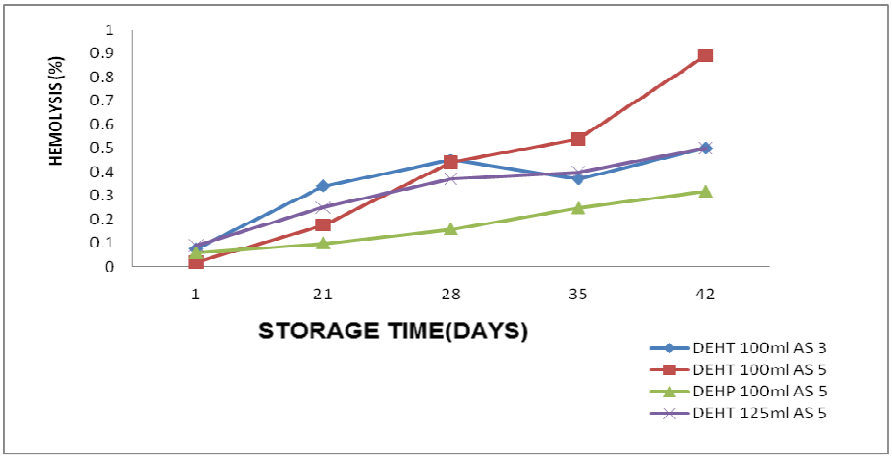


Figure 2
DEHT PVC bags- Hemolysis(%) of RBCs in various anticoagulant solutions.



The increase in volume of AS 5 solution 125 ml, used in this study was selected such that it did not result in a decrease of the accepted haematocrit level of 50-70%, for leuco reduced RBCs. (Standard requirement, AABB,EU etc). The storage performance of RBCs in DINCH and DEHT plasticised PVC bags depend on the additive solutions used. Storage of RBC in DINCH and DEHT containers with 100ml AS 5 resulted in increased hemolysis, with some units exceeding the maximum allowable level of 0.8% on day 42 of storage. Hemolysis was much lower with 125ml AS 5 and 100ml AS 3. During storage in AS 5 100ml, changes in MCV were observed which was less pronounced in the presence of 125ml AS 5 and 100ml AS 3 in the two types of bags. The better performance of RBCs stored in 125ml AS 5 could be due to the presence of higher amounts of mannitol, glucose and adenine in AS 5. Adenine provides a substrate for ATP synthesis resulting in improved viability. Mannitol acts as a membrane stabiliser and reduces hemolysis. Dextrose provides energy for ATP synthesis. Citrate and phosphate in AS 3 acts as buffer to control fall in p H from the generation of lactic acid due to glycolysis.

CONCLUSION

The present study is a comparative assessment of the suitability of DEHT and DINCH plasticised PVC bags for the storage of RBCs in the presence of AS3 and AS 5 RBC preservative solutions. The studies show that RBCs could be stored in DEHT and DINCH plasticized bags for up to 42 days maintaining acceptable hemolysis and other quality parameters using 125ml AS 5 and 100ml AS 3 additive solutions.

SUMMARY

DEHT and DINCH plasticized PVC bags are found suitable for the 42 days storage of RBC maintaining the quality requirements. The storage performance found depend on the additive solutions used.

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