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Assessment of Patient Exposure to Leachables from Lyophilized Drug Formulations Following Reconstitution, Storage, and Administration via Polymeric Packaging/Delivery Systems

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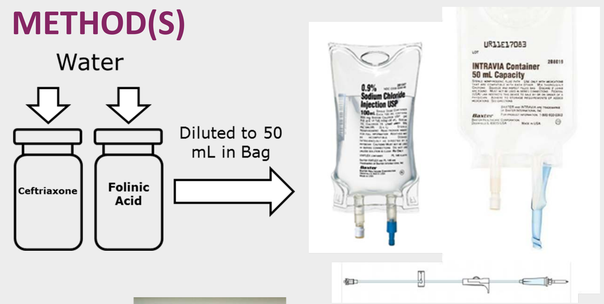
PURPOSE

It has been demonstrated that drug products stored as a lyophilized solid have an increased propensity to leach substances from their primary packaging system, typically a glass vial sealed with a rubber stopper, as compared to aqueous liquid formulations stored in the same configuration. However, no studies have been performed to determine if these leachables are introduced to the patient during reconstitution and contact with systems used to store or administer the reconstituted product, such as syringe, pumps, or IV bags. Therefore, the purpose of this study was to provide insight into this matter by testing the hypothesis that leachables present in a lyophilized drug product stored in its primary vial/stopper packaging configuration would be introduced to the patient in a reduced amount, or not at all, following reconstitution and after contact with a secondary and/or tertiary polymeric delivery system(s) for some period of time.

METHOD(S)

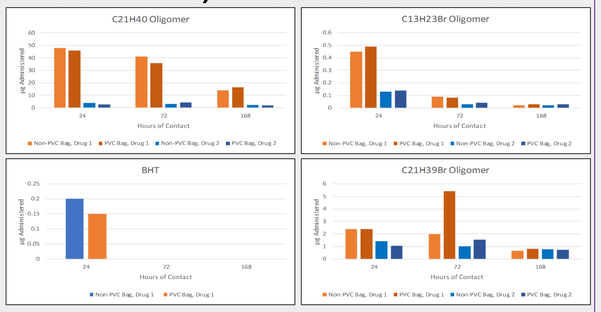


Variables Assessed:

- PVC and non-PVC bags.
- Contact durations of 4 hours – seven days.
- Short-term exposure to an administration set.
- Storage at ambient and 5 °C.

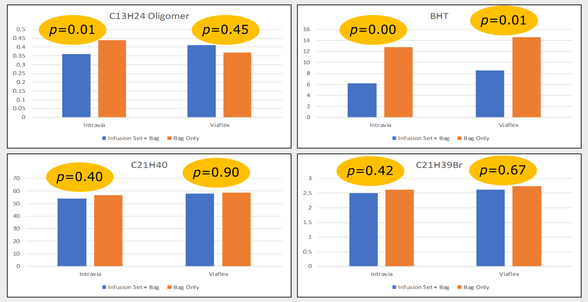
RESULTS

Does the Bag's Composition (Plasticized PVC Versus non-PVC) Affect the Mass Administered?



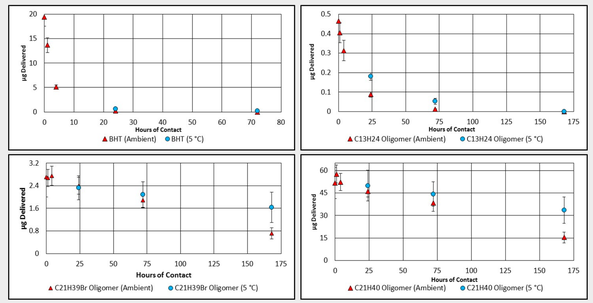
- In general, no obvious or statistically significant difference ($p >> 0.05$) was evident between the PVC and non-PVC bags.
- This is inconsistent with previous reports of API absorption by PVC versus non-PVC materials.

What is the Impact of Short-term Contact With an Administration Set?



- BHT was affected by short-term contact with the administration set.
- However, none of the butyl rubber oligomers had a statistically significant difference when comparing solutions that had contacted the set versus those that had contacted the bag only.

What Impact Do Time and Temperature have on Mass Administered?



- Trends were quite different between compounds with significantly different physical properties.
- As expected, lowering temperature reduces the rate of loss from solution.
- Otherwise, general trends were consistent between temperatures.

What Impact Does the Drug Product's Formulation Have on Mass Administered?

Compound	Folinic Acid			Ceftriaxone		
	1 Day	3 Days	7 Days	1 Day	3 Days	7 Days
$C_{13}H_{24}$ Oligomer	15	2	0	3	0	0
$C_{13}H_{23}Br$ Oligomer	24	4	1	6	1	1
$C_{21}H_{40}$ Oligomer	81	67	27	59	66	35
$C_{21}H_{39}Br$ Oligomer	95	73	28	64	68	40

- Percent loss values were used in this assessment to normalize differences in the intrinsic amount of each leachable in each drug product.
- Although this was not investigated extensively, it is reasonable to expect similar highly aqueous products with no solubilizing agents to have similar results due to lack of affinity of hydrophobic leachables for them.

Differences in Temperature as a Function of Arrhenius Predictions

- Using the Q10 approach, such as outlined in the ASTM Standard, the expected magnitude difference can be estimated.

Compound	Mean μg Administered		p	Mean μg Administered		p
	1 Day (Ambient)	3 Days (5 °C)		3 Day (Ambient)	7 Days (5 °C)	
$C_{13}H_{23}Br$ Oligomer	0.5	0.4	0.21	0.08	0.07	0.09
$C_{21}H_{40}$ Oligomer	46.9	42.7	0.63	38.4	33.6	0.28
$C_{21}H_{23}Br$ Oligomer	2.4	2.0	0.19	1.9	1.6	0.32

- The comparability in the data for the 1 and 3 day ambient/5 °C data (3 fold difference) and the 3 and 7 ambient/5 °C (2.3 fold difference) illustrates the applicability of this relationship.

CONCLUSION(S)

1. Lyophilized drug formulations have an increased propensity to leach substances from their primary packaging system as compared to highly aqueous media stored in the same system.
2. The mass of leachables present in a lyophilized formulation that are introduced to the patient may be reduced or completely eliminated after reconstitution, storage and/or administration.
3. However, in some cases, most or all of the leachable mass in the vial may be introduced to the patient.

FULL PAPER

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