

Introduction

Cremophor (polyoxyethylene castor oil derivative) is a widely used excipient in injectable formulations for poorly soluble small molecules, including anticancer drugs such as paclitaxel^[1] and docetaxel. It significantly enhances the solubility of these drugs by forming micellar structures, typically increasing solubility by several orders of magnitude. However, the clinical application of Cremophor is constrained by dose-dependent allergic reactions, which are also a concern in preclinical research^[2,3]. Beagle dogs exhibit marked species-specific sensitivity to Cremophor-based excipients. This approach aims to clarify the risks in preclinical research in dogs and provide detailed data on injectable formulations for drug discovery.

Methods

The study aimed to evaluate the safety of Cremophor using beagle dogs, cynomolgus monkeys, mini pigs and rabbits. Beagle dogs were administered Cremophor through various routes (intravenous (IV), intramuscular (IM), and subcutaneous (SC)) at different dosages, as detailed in Table 1. Additionally, cynomolgus monkeys and mini pigs received Cremophor via the IV route for comparative clinical observations, as shown in Table 2. Cremophor concentrations expressed as % w/v (g/100 mL) throughout.

Table 1: Beagle Dog Multi-Route Administration Experimental Design

Route	Formulation	Concentration (% w/v)	Volume	Dose Level	Animal No.
IV	Cremophor EL	5%	1 mL/kg	50 mg/kg	2
	Cremophor ELP	5%	1 mL/kg	50 mg/kg	2
IM	Cremophor EL	10%	0.2 mL/kg	20 mg/kg	3
	Cremophor ELP	10%	0.2 mL/kg	20 mg/kg	3
	Cremophor EL	20%	0.5 mL/kg	100 mg/kg	3
	Cremophor ELP	20%	0.5 mL/kg	100 mg/kg	3
SC	Cremophor EL	15%	5 mL/kg	750 mg/kg	3
	Cremophor ELP	15%	5 mL/kg	750 mg/kg	3

Table 2: Cross-Species IV Safety Assessment Design

Species	Formulation	Concentration (% w/v)	Volume	Dose Level	Animal No.
Cynomolgus Monkeys	Cremophor EL	20%	2 mL/kg	400 mg/kg	4
Mini pigs	Cremophor EL	20%	2 mL/kg	400 mg/kg	4
Rabbits	Cremophor EL	20%	2 mL/kg	400 mg/kg	4

Conclusion

Cremophor-based excipients are not suitable for IV administration in Beagle dogs, but they can be safely applied via IM and SC routes. Furthermore, assessments in non-canine species further reinforces the feasibility of IV administration of Cremophor-based excipients, providing practical references for drug discovery and development across different species.

References

[1] Zhang JA, Anyarambhatla G, Ma L, Ugwu S, Xuan T, Ardone T, Ahmad I (2005) Development and characterization of a novel Cremophorw EL free liposome-based paclitaxel (LEP-ETU) formulation. Eur J Pharm Biopharm 59:177–187
[2] Shayne Cox Gad. Tolerable Levels of Nonclinical Vehicles and Formulations Used in Studies by Multiple Routes in Multiple Species With Notes on Methods to Improve Utility. International Journal of Toxicology.2016
[3] Seshadri Neervannan. Preclinical formulations for discovery and toxicology: physicochemical challenges. Expert Opin. Drug Metab. Toxicol. (2006) 2(5):715-731

Professional veterinarians participated in the evaluation, which primarily focused on assessing allergic reactions, including clinical signs of discomfort or pain such as pruritus, erythema, and swelling, particularly in key observation sites. All experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of WuXi AppTec.

Results

1. IV Administration Risk Assessment
Following slow IV injection of 5% Cremophor EL (1 mL/kg), dogs exhibited severe systemic allergic reactions, characterized by generalized erythema and systemic swelling, necessitating urgent veterinary intervention.

2. IM Administration Risk Assessment

Table 3: Safety Thresholds for Intramuscular Cremophor Administration in Beagle Dogs

Dose	Formulation	Adverse reactions	Recommendation
Low Dose 20 mg/kg (10%*, 0.2 mL/kg)	Cremophor EL	✔ Well tolerated	➤ SAFE ZONE: ≤20%* + ≤0.5 mL/kg
	Cremophor ELP	✔ Well tolerated	
High Dose 100 mg/kg (20%*, 0.5 mL/kg)	Cremophor EL	⚠ Transient pruritus	➤ Tolerance: Cremophor ELP > Cremophor EL
	Cremophor ELP	✔ Well tolerated	

Comment: *% w/v

3. SC Administration Risk Assessment

Table 4: Safety Thresholds for High-Dose Subcutaneous Cremophor in Beagle Dogs

Dose	Formulation	Adverse reactions
750 mg/kg (15% w/v, 5 mL/kg)	Cremophor EL	✔ Well tolerated
	Cremophor ELP	✔ Well tolerated

4. Species-Specific Tolerance Assessment

Table 5: Species-Specific Compatibility of IV Cremophor: Hypersensitivity Alert in Beagle dogs

Species	Tolerance Level	Adverse reactions
Beagle Dogs	✖ High Sensitivity	Systemic allergic reactions at 50 mg/kg (IV)
Cynomolgus Monkeys	✔ Well tolerated	No reaction at 400 mg/kg (IV)
Mini pigs	✔ Well tolerated	No reaction at 400 mg/kg (IV)
Rabbits	✔ Well tolerated	No reaction at 400 mg/kg (IV)



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