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Nature of Precipitation Resulted from Intravenous Drugs Incompatibility

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ABSTRACT

In critical care, the co-administration of intravenous drugs often leads to physical incompatibilities, resulting in harmful precipitates. This study evaluated the nature of drug-induced precipitation in terms of size, shape, and quantity. Twelve drugs previously reported to be incompatible were tested with infusion fluids. Particle detection was conducted using an Olympus CX41 microscope with a 1 µm detection limit, enhanced by darkfield microscopy for better sensitivity. Particle size was analyzed using Feret's diameter via the Optilab imaging system. Precipitates ranged from 5–150 µm, with smaller particles (<10 µm) seen in furosemide and subvisible particles (10–50 µm) in cefotaxime, chloramphenicol, and paracetamol. Visible particles were noted in acyclovir, ampicillin, meropenem, phenobarbital, and phenytoin. Most macro-precipitates were acicular, while micro-precipitates tended to be irregular. Particle counts ranged from 80 to 2,000 particles/mL. The findings highlight the clinical risk of particulate contamination due to drug incompatibilities, emphasizing the need for careful medication management.

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1. INTRODUCTION

Critical care patients often receive a lot of intravenous medication which potentially results in incompatibility (Hanifah *et al*., 2018; Koller *et al*., 2020). Intravenous incompatibility may result in precipitations, which would be harmful to patients (Benlabed *et al*., 2019; Négrier *et al*., 2021; Marsilio *et al*., 2016). Particulate contamination from IV medication under sterile preparation is mostly caused by intrinsic factors (Doessegger *et al*., 2012; Molina *et al*., 2022). These particles mostly resulted from drug incompatibility, precipitation from parenteral nutrition, also the packaging and particularly glass container elements (Hanifah *et al*., 2019; Hanifah *et al*., 2020; Langille, 2013). Therefore, patients in the ICU have great possibilities to get negative effects from incompatibilities.

Mortality caused by the precipitation had been reported in the NICU resulting from the incompatibility of ceftriaxone and ringer lactate (Christensen *et al*., 2021). Drug precipitation induced by the incompatibility of ceftriaxone-calcium and calcium-phosphate is a great example of the significant risk of precipitation. Calcium is commonly found in ringer lactate and parenteral nutrition admixture as calcium gluconate or calcium chloride (Hanifah *et al*., 2021). Among 41 infants who get parenteral nutrition, 37000 particles between 2 and 100 um in one day, in which to lipid emulsion as many as 80% (Worthington *et al*., 2021). A recent study predicted that 5 million particles between 2 and 100 um arise from parenteral nutrition solution (Worthington *et al*., 2021). Accordingly, patients receiving concurrent incompatible drugs or parenteral nutrition should be paid more attention following the number of particles they got instead of particle load from other sources.

The dangers of particles were first recognized; there is currently no evidence that particulate matter is beneficial, but it can have detrimental effects. Those effects have been observed such as local reactions, thrombus and embolism-induced blood vessel occlusion, hypoperfusion, microvascular disturbance, inflammatory response, granuloma, altered body system function (immunologic or neoplastic response), tissue damage, and even internal organ failures (Hantrakool *et al*., 2022). Particles might not work well with a patient's vascular system, changing the immune system and decreasing the effectiveness of medications (Liu & Hutchinson, 2024).

Considering the abovementioned showed the reason why the particulate contamination is a big matter for intravenous drug administration. However, studies on particulate matter seem not to happen as quickly as drug discovery or studies in pharmacotherapy. A lot of studies investigate contamination from intrinsic factors, but studies that evaluated particulate contamination are limited (Liu & Hutchinson, 2024; van den Berg *et al*., 2024). This may cause less awareness of practitioners or pharmacists toward this matter. Therefore, a study on contamination, particularly in physical or particulate matter regarding incompatibility, is likely worthwhile. This study investigated the nature of precipitation, including size, shape, and quantity resulting from incompatibility. This study also tried to confirm the source and risk of particulate contamination on intravenous medication. This will bring a recommendation on hazards and how to minimize the risk of particulate contamination in hospital settings, particularly in the ICU.

2. METHODS

This study used 12 different drugs combined with infusion fluids resulting in incompatibility as in previous reports (**Table 1**). The medications were mixed in a 1:1 ratio in volume. 0.025 mL samples were drawn and checked under microscopy to see the nature of precipitation. An Olympus CX41 microscope, with a 1 µm detection limit, was used to find particles. An

Olympus CX41 microscope equipped with a UIS (Universal Infinity System) optical system which was employed with the illuminator (Abbe Condenser) includes an integrated 6V 30W halogen light. To improve the illumination and sensitivity, a black opaque disk was positioned beneath the condenser on the light's upper surface and subjected to dark field microscopy. The sophisticated imaging technology from Optilab was used to measure the particle size. Feret's diameter and fiber length were used to calculate the particle size.

Table 1. The drugs and infusion fluids which is evaluated for incompatibility.

Drug	Solvent	Final concentration
Acyclovir 50 mg/mL	Dextrose 5%	10 mg/mL
Ampicillin 1000 mg	Dextrose 5%	200 mg/mL
Cefotaxime sodium 1000 mg	Normal Saline	200 mg/mL
Chloramphenicol sodium succinate 1000 mg	Normal Saline	200 mg/mL
Dexamethasone sodium phosphate 5 mg/mL	Dextrose 5%	1 mg/mL
Furosemide sodium 20 mg/2 mL	Dextrose 5%	10 mg/mL
Gentamicin sulfate 80 mg/2 mL	Dextrose 5%	40 mg/mL
Phenytoin sodium 100 mg/2 mL	Dextrose 5%	10 mg/mL
Meropenem 500 mg	Dextrose 5%	50 mg/mL
Paracetamol 1000 mg/100 mL	Ringer Asetat	100 mg/mL
Phenobarbital sodium 200 mg/2 mL	Dextrose 5%	10 mg/mL
Ranitidine HCl 50 mg/2 mL	Dextrose 5% in RL	25 mg/mL

3. RESULTS AND DISCUSSION

Figures 1 and **2** show representative particulate matter observed in specific combinations of drugs and the infusion effluent. In some cases, the quantity of particulate matter was quite large as seen in acyclovir, meropenem, and phenytoin. Precipitates range in size from 5 to 150 µm. Tiny particles, as in furosemide, which are less than 10 µm. The precipitation of cefotaxime, chloramphenicol, and paracetamol allowed for the identification of subvisible particles with sizes ranging from 10 to 50 µm. Particles visible in the acyclovir, ampicillin, meropenem, phenobarbital, and phenytoin precipitates. This is consistent with the results of Jack *et al*. (2010), who found that most of the particles had a diameter of between 5 and 50 µm and ranged in size from 5 µm to more than 100 µm. According to Veggeland & Brandl (2010), the most frequent classification consists of two types: (1) macro-precipitation, which is typically visible using light with a size of greater than 50 µm, and (2) micro-precipitation, which is visible under a microscope with a size of less than or 50 µm. According to this classification, acyclovir, ampicillin, dexamethasone, meropenem, phenytoin, and phenobarbital showed signs of macro-precipitation, whilst the other drugs showed signs of micro-precipitation.

Particle size has been proven to influence the risk. Any particle larger than the capillary diameter will occlude the capillary bed. Also, when the particle comes up into the venous artery, it might lodge the vessel when the particle is larger than the vasculature diameter. The smaller the size, the more difficult to overcome (Liu & Hutchinson, 2024). It is linked to the distribution of particles in the vasculature and tissue is influenced by the size or diameter of particles as well. After intravenous delivery, the particulate contamination enters the vein which increases the direction of blood flow, the particle can travel through the venous system and reach the heart and lungs. Particles smaller than 10 microns commonly get in capillary and trap in tissue. Particle size 0.1-10 potentiates immunogenicity risk, 50-200 micro: in the

mesenteric artery (Hantrakool *et al*., 2022). Particles>7 microns tend to be trapped in the lung, while those <7 will be retained in the liver, spleen, or kidney (Hantrakool *et al*., 2022).

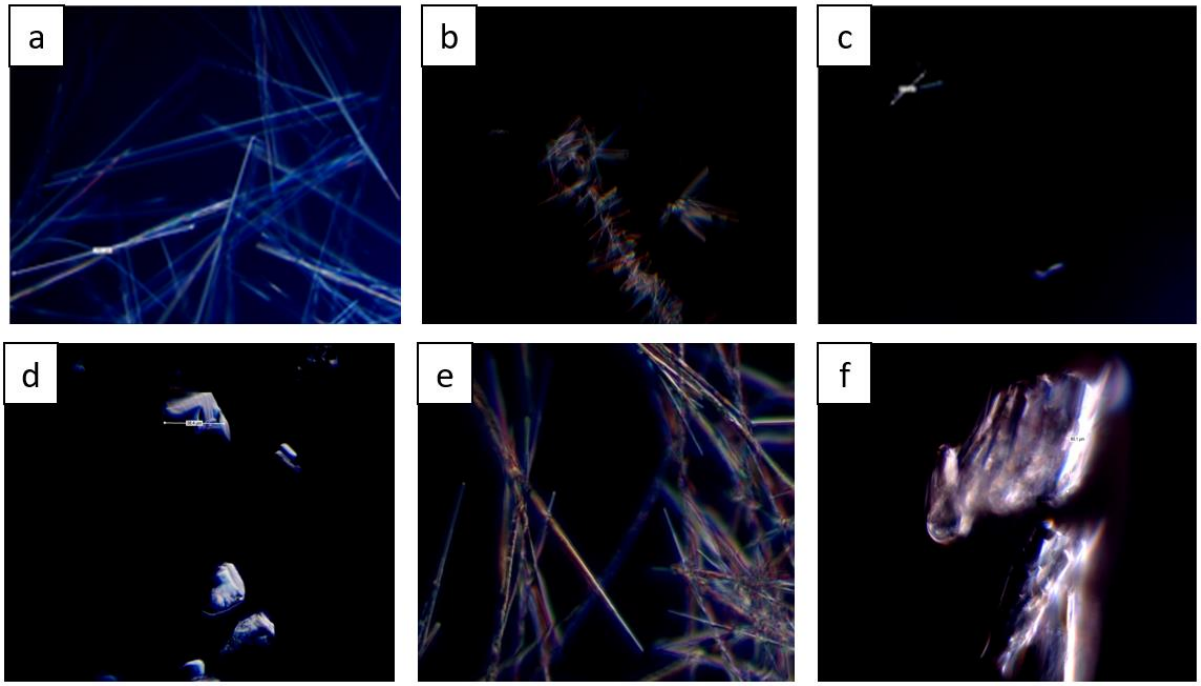

Figure 1. Images of visible particles (>50 µm) precipitation after injection delivery during simultaneous infusion for Acyclovir (40X) (a); Ampicillin (40X) (b); Dexamethasone (40X) (c); Meropenem (40X) (d); Phenytoin (40X) (e); and Phenobarbital (40X) (f).

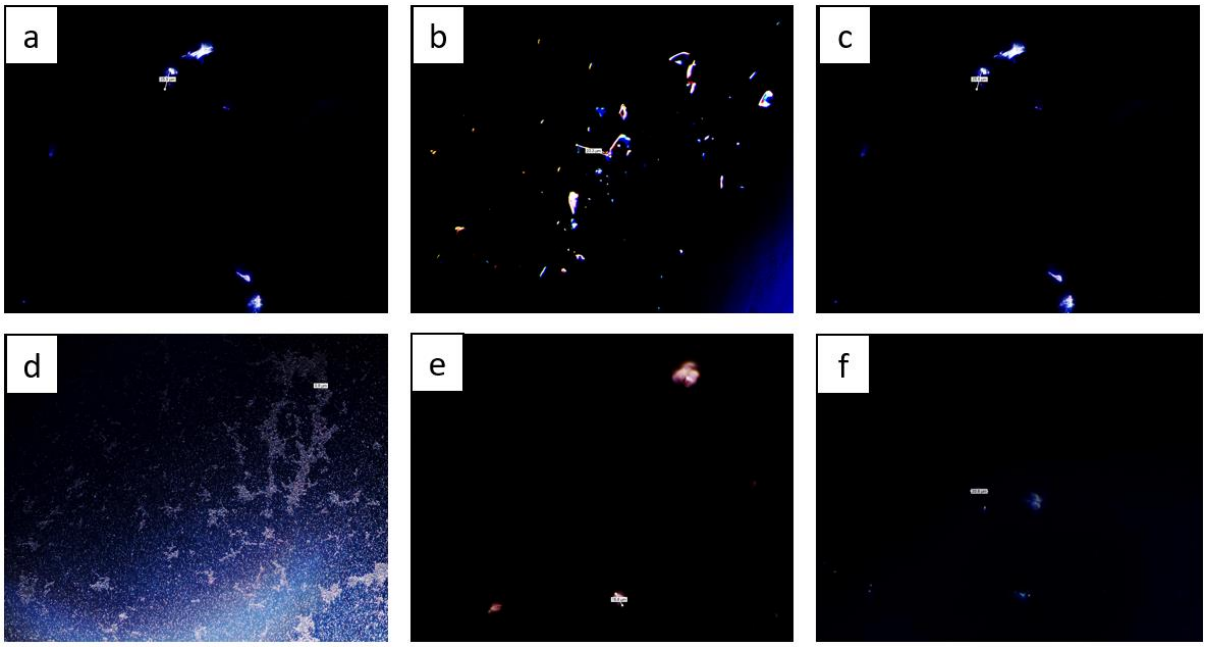

Figure 2. Images of subvisible particles (<50 µm) precipitation after injection delivery during simultaneous IV infusion for Cefotaxime (40X) (a); Chloramphenicol (40X) (b); Gentamicin (40X) (c); Furosemide (40X) (d); Paracetamol (40X) (e); and Ranitidine (40X) (f).

Most of the macro-precipitates, as seen in Figures 1 and 2, had acicular shapes; very few had irregular ones. Micro-precipitates frequently have irregular forms. Given that the samples' particle counts ranged from 2 to 50 particles per 0.025 milliliters, there would be

80–2000 particles per milliliters. Many macro-precipitates were either columnar (phenobarbital and dexamethasone) or acicular (acyclovir, ampicillin, and phenytoin, for example). Others, like Meropenem, were erratic. Micro-precipitates containing drugs such as furosemide, paracetamol, and chloramphenicol frequently had the most asymmetrical forms. Hard particles that are non-spherical and irregular in shape are more prone to occlude in a vessel (Langille, 2013). Soft particles, on the other hand, tend to be spherical, flexible, and malleable and thus are more prone to disperse widely within the vessel. The pliable particulate can cause embolism, but it is reversible (Hantrakool *et al*., 2022; Febres-Aldana & Howard, 2018).

Moreover, **Figure 3** indicates that the particles' spectra are suggestive of organic medicine molecules (carbon [C], oxygen [O], sodium [Na], calcium [Ca], potassium [P], and chloride [Cl]) as the component of the pharmaceutical sample, confirming the source of the particles. Furthermore, none of the metals that would be predicted if contaminated—silicon [Si], aluminum [Al], zinc [Zn], or iron [Fe]—are showing up as peaks in the spectra. It concludes that the particle is not coming from the glass or packaging.

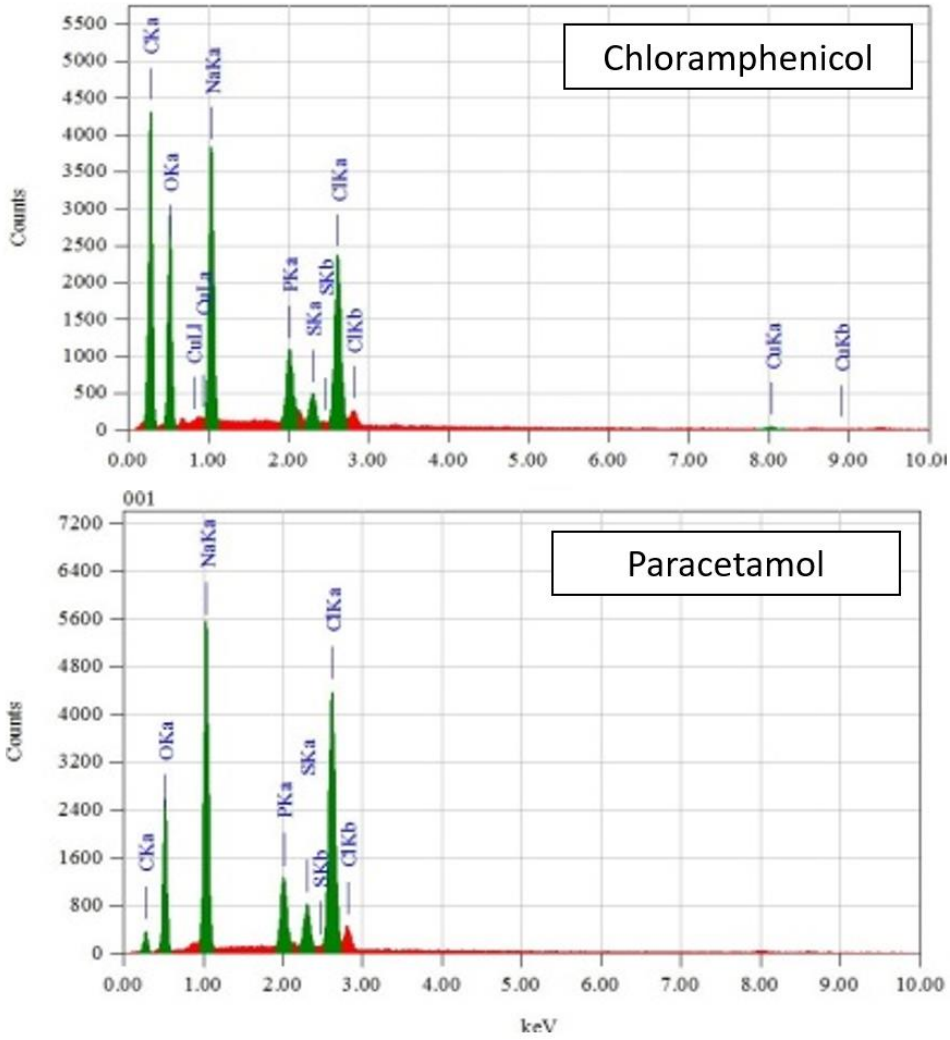

Figure 3. Particle elements in the sample of incompatibility which indicative of organic drug molecules (carbon [C], oxygen [O], sodium [Na], calcium [Ca], potassium [P], and chloride [Cl]), with the spectra showing no peaks indicative of silicone [Si], aluminum [Al], zinc [Zn] or iron [Fe], which would be expected if contaminated with rubber or glass.

In considering the number of particles, it is quite large. If there were 50 particles in acyclovir in the sample volume (0.025 mL) examined by microscope, there would be 4,000 particles injected into the patient at each single time of administration (STA) from each 2 mL dose. Therefore, the patient may receive about 8,000 particles per day from one type of drug. Under microscopy, much precipitation was observed with this usually too heavy to permit the particles to be counted. Therefore, the estimate of 8,000 particles is very conservative. If the patient received other drugs, also heavily laden with particles, the total daily load would increase. This number is less than earlier reports which stated that patients in ICUs acquire particulate contamination of more than 1 million particles >2 µm per day and more than 10 million particles >2 µm during a hospital stay (van den Hoogen *et al*., 2006; Licina *et al*., 2016). The number of particles observed in the current study may be lower than the actual number of particles received in the body, as this study was undertaken under more carefully controlled circumstances than in the hospital. Jack concluded that the number of particles is influenced by the complexity of the applied admixture (Jack *et al*., 2010).

Although the evidence of hazardous particulate infusion is not sufficient, some scholars have proven the contribution of particles to deadly effects. Some scholars assume that the clinical risk of particles correlated with tolerance of phagocytosis or RES system. This may also be influenced by space consumption to induce clinically significant. For example, pulmo thromboembolism will happen when 30-50% of the occluded (Langille, 2013). Various particle types in origins, shape, size, or quantity also influence the significance of risk (Hantrakool *et al*., 2022; Liu & Hutchinson, 2024). So far, future research necessitates further investigation into the kinetic, pathophysiology of various particle types associated with clinical risk.

4. CONCLUSION

This study has shown that incompatibility medications result in significant particulate matter with macro and micro precipitates. The incompatibility also results in various sizes, shapes, and very large numbers which have potentially harmful and deadly effects on patients. Incompatibility prevention will be significant in reducing particulate contamination.

5. AUTHORS' NOTE

The authors declare that there is no conflict of interest regarding the publication of this article. Authors confirmed that the paper was free of plagiarism.

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7. REFERENCES

Benlabed, M., Perez, M., Gaudy, R., Genay, S., Lannoy, D., Barthelemy, C., and Decaudin, B. (2019). Clinical implications of intravenous drug incompatibilities in critically ill patients. *Anaesthesia Critical Care & Pain Medicine*, *38*(2), 173-180.

Christensen, M. L., Zareie, P., Kadiyala, B., Bursac, Z., Reed, M. D., Mattison, D. R., and Davis, R. L. (2021). Concomitant ceftriaxone and intravenous calcium therapy in infants. *The Journal of Pediatric Pharmacology and Therapeutics*, *26*(7), 702-707.

Doessegger, L., Mahler, H. C., Szczesny, P., Rockstroh, H., Kallmeyer, G., Langenkamp, A., and Famulare, J. (2012). The potential clinical relevance of visible particles in parenteral drugs. *Journal of Pharmaceutical Sciences*, *101*(8), 2635-2644.

Febres-Aldana, C. A., and Howard, L. H. (2018). Fatal Sickling Triggered by Massive Foreign Particle Embolism: A Case Report of Unrecognized Indwelling Venous Catheter Drug Abuse in Sickle Cell Disease. *The American Journal of Forensic Medicine and Pathology*, *39*(2), 152-156.

Hanifah, S., Ball, P., and Kennedy, R. (2018). Medication incompatibility in intravenous lines in a Paediatric Intensive Care Unit (PICU) of Indonesian hospital. *Critical Care & Shock*, *21*(3), 114-123.

Hanifah, S., Maulidani, Y., Nugroho, B. H., and Sari, C. P. (2019). All-in-one versus lipid-free parenteral nutrition for premature infants: visual, pH, and particle size analyses. *Nutricion Hospitalaria*, *36*(6), 1-4.

Hanifah, S., Maulidani, Y., Nugroho, B. H., and Sari, C. P. (2021). Provision of standardized all-in-one parenteral nutrition (AIO-PN) for very preterm neonates: Evaluation at room and cold temperatures*. Journal of Pharmacy and Bioallied Sciences*, *13*(1), 26-30.

Hanifah, S., Nugroho, B., and Chabib, L. (2020). Compatibility of acetaminophen with central nervous system medications during simulated Y-site injection. *Anaesthesiology Intensive Therapy*, *52*(1), 23-27.

Hantrakool, S., Kumfu, S., Chattipakorn, S. C., AND Chattipakorn, N. (2022). Effects of particulate matter on inflammation and thrombosis: past evidence for future prevention. *International Journal of Environmental Research and Public Health*, *19*(14), 8771.

Jack, T., Brent, B. E., Boehne, M., Müller, M., Sewald, K., Braun, A., Wessel, A., and Sasse, M. (2010). Analysis of particulate contaminations of infusion solutions in a pediatric intensive care unit. *Intensive Care Medicine*, *36*, 707-711.

Koller, A. K., Krebs, S., and Dörje, F. (2020). Medication safety in intravenous therapy: a compatibility study of clonidine with drugs frequently used in intensive care. *Pharmaceutics*, *13*(1), 21.

Langille, S. E. (2013). Particulate matter in injectable drug products. *PDA Journal Pharmaceutical Science and Technology*, *67*(3), 186-200.

Licina, D., Bhangar, S., Brooks, B., Baker, R., Firek, B., Tang, X., and Nazaroff, W. W. (2016). Concentrations and sources of airborne particles in a neonatal intensive care unit. *PloS One*, *11*(5), e0154991.

Liu, F., and Hutchinson, R. (2024). Visible particles in parenteral drug products: A review of current safety assessment practice. *Current Research in Toxicology*, 7, 100175.

Marsilio, N. R., Silva, D. D., and Bueno, D. (2016). Drug incompatibilities in the adult intensive care unit of a university hospital. *Revista Brasileira de Terapia Intensiva*, *28*, 147-153.

Molina, S. A., Davies, S. J., Sethi, D., Oh, S., Durand, N., Scott, M., and Clarke, D. (2022). Particulates are everywhere, but are they harmful in cell and gene therapies?. *Cytotherapy*, *24*(12), 1195-1200.

Négrier, L., Martin Mena, A., Lebuffe, G., Odou, P., Genay, S., and Décaudin, B. (2021). Strategies to prevent drug incompatibility during simultaneous multi-drug infusion in intensive care units: a literature review. *European Journal of Clinical Pharmacology*, *77*, 1309-1321.

van den Hoogen, A., Krediet, T. G., Uiterwaal, C. S., Bolenius, J. F., Gerards, L. J., and Fleer, A. (2006). In-line filters in central venous catheters in a neonatal intensive care unit. *Journal of Perinatal Medicine*, *34*(1), 71-74.

Veggeland, T., AND Brandl, M. (2010). Evaluation of a simple method for visual detection of microprecipitates in blends of parenteral drug solutions using a focused (Tyndall) light beam. *International Journal of Pharmaceutical Compounding*, *14*(1), 78-81.

Worthington, P., Gura, K. M., Kraft, M. D., Nishikawa, R., Guenter, P., Sacks, G. S., and Committee, A. P. S. (2021). Update on the use of filters for parenteral nutrition: an ASPEN position paper. *Nutrition in Clinical Practice*, *36*(1), 29-39.