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ORIGINAL RESEARCH

Medication Safety in Intravenous Therapy: Compatibility of Etoposide with Frequently Drugs Used in Tumour Critical Care During Simulated Y-Site Administration

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Objective: Etoposide is an antineoplastic agent widely used to treat pediatric and adult cancers. Critically ill patients are expected to receive several intravenous pharmaceutical drugs while admitted to hospitals. When compatibility data are available, intravenous drugs may be administered simultaneously through the Y-site. This study aimed to determine the compatibility of etoposide during simulated Y-site administration with 45 continuous-infusion drugs that are commonly administered in tumor critical care units.

Methods: Etoposide was diluted to a concentration of 0.25 mg/mL in 0.9% sodium chloride (NS) and other intravenously tested drugs were reconstituted according to the manufacturer's recommendations to the final clinical desired concentrations. Y-site administration was simulated in vitro by mixing 5 mL etoposide with other diluted intravenous medications under aseptic conditions in a 1:1 ratio. Compatible solutions were withdrawn at certain time intervals (0, 1, 2, 4 hours) after mixing and tested visually, using a Tyndall beam, pH, turbidity, insoluble particles, and UV absorption as measures of compatibility.

Results: Etoposide was compatible with 38 (84%) of the 45 drugs tested within four hours. Glutathione and human granulocyte colony-stimulating factor immediately showed incompatibility with etoposide. Within 1 h, four medications (cefuroxime sodium, ilaprazole sodium, mycophenolate, and xuebijing) were incompatible. Within 4 h, one medications (ceftazidime) were also found to be incompatible with etoposide under observation.

Conclusion: Seven of the 45 common medications in tumor critical care tested with etoposide were incompatible within 4 h. If co administration is inevitable and the drug is infused through a port catheter, a larger volume of saline (NS) or dextrose 5% in water (D5W) should be used to flush the port catheter before and after the etoposide infusion to clean the lumen of the port catheter.

Keywords: compatibility, Y-site administration, intravenous, etoposide, critical care

Introduction

Etoposide is a chemotherapeutic agent used in the treatment of a variety of solid and hematologic malignancies in adult and pediatric patients, primarily including various leukemias, lymphomas, sarcomas, neuroblastomas, rhabdoid, and germ cell tumors.[1–3] It can be used as a single agent but is more commonly used in combination with multi-agent regimens to treat several malignancies, including testicular embryonic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), non-Hodgkin malignant lymphoma, and acute leukaemia.[4–6]

Etoposide is an irritant that is known to have vesicant properties in higher concentrations or larger volumes, and an intravenous flare response may be observed after sustained infusion.[7] Case reports described reactions associated with Etoposide infusion, such as myelosuppression, hypotension, hair loss, and gastrointestinal symptoms (nausea, vomiting,

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diarrhea, constipation, mucositis, and anorexia).[8–10] Therefore, knowledge of the physicochemical characteristics of the drug is fundamental in the selection of a suitable VAD to reduce the risk of vascular damage, thereby avoiding local side effects such as phlebitis and thrombosis caused by incorrect or incompatible combination administration.[7,11] In addition to the administration of etoposide, critically ill cancer patients with adverse drug reactions (ADRs) often simultaneously receive a number of other drugs (including for sedation, antiemetic, anti-inflammation, analgesia, and vasopressor support) via continuous infusion.[12] Since the patients often have limited venous access to deliver all of the intravenous medications, this leads to delivery of several intravenous drugs including etoposide, which possibly has contact with other drugs via a three-way stopcock or infusion connector, ie Y-site.[13] For Y-site infusions, drugs must be physicochemical compatible, meaning that no precipitation, no change of colour or no gas formation. Otherwise, these drugs must be transfused through separate pipelines or staggered according to priority, infusion time, and dosing intervals.[14,15] Physicochemical incompatibility can form precipitates, change of active drugs or formation of toxic compounds that can lead to catheter obstruction, venous irritation, pulmonary or kidney embolism, infarction, and even death, as well as activate the immune system and lead to systemic inflammatory response syndrome.[16–18] Another showed that physicochemical incompatibilities represented 19 out of 102 (18.6%) recorded nursing acts during a 30-day period in a clinical ward.[19] The clinical impact of drug incompatibilities might be particularly deleterious in critically ill patients. However, information on the compatibility of etoposide remains incomplete and insufficient, making its use with multiple drugs via the Y-site challenging, especially those that require prolonged intravenous infusion. There is no standard protocol or consensus on which tests should be performed to judge compatibility/incompatibility of intravenous drugs administered by Y-site infusion.

Etoposide can be administered via a slow intravenous infusion with normal final concentrations ranging from 0.2 to 0.4 mg/mL.[20] To shed light on the compatibility of etoposide, this study analyzed 0.25 mg/mL etoposide, which is a general representative concentration for clinical use, and with 45 drugs frequently used in the cancer critical care units of The First Affiliated Hospital of USTC, during Y-site administration. The physicochemical stability of the admixtures was assessed by visual examination, Tyndall beam, pH and turbidity changes, particle limits, and spectroscopic absorption at 550 nm and 420 nm over 4 h. Subsequently, we evaluated the sensitivity and accuracy of these methods for the quick and easy compatibility testing of intravenous fluids in a hospital pharmacy setting.

Materials and Methods

Sample Preparation

The 45 drugs were collected from the First Affiliated Hospital of the USTC as frequently used intravenous drugs in tumor critical care units. Drug specifications, manufacturers and specifications, lot number, diluent, and concentration of each drug according to the clinical drug concentration (Table 1). The drug solutions of etoposide and the combination partners were prepared in a laminar airflow hood, a 5-mL sample of etoposide was combined with another 5-mL sample of each of the tested intravenous drug solutions and cultured in a 15-mL colorless borosilicate glass screw-cap tube to simulate the inline mixing through a Y-injection site at a ratio of 1:1 in vitro.[12] Before mixing, each of the sample solutions was passed through a 0.22 mm filter in the filter syringe when it was introduced into the tube to reduce the background noise of the particles.

All solutions were mixed and analyzed under ambient laboratory conditions (22–25°C) with no clinical or in vivo studies. The compatibility of the samples was analyzed based on visual characteristics, Tyndall beam, pH and turbidity changes, and formation of subvisual particles and spectroscopic changes at absorption wavelengths of 420 and 550 nm.

Visual Inspection

The samples were extracted directly after mixing and after 1 h, 2 h, and 4 h. Visual examinations of all admixtures were performed by unaided eye against white and black backgrounds, according to the Chinese Pharmacopoeia (Ch.P) 2020 edition.[21] Incompatibilities which defines changes in color, precipitation, gas formation, and visual particulate matter compared to the baseline of the original solution within 4 h.

Table 1 Drugs Included in the Study: Manufacturer, Diluent, and Concentration

Drug	Manufacturer (Lot)	Diluent	Concentration (mg/mL)	P/C
Aciclovir Sodium	Furen Medicines Group (20230293)	NS	1.36	C
Ambroxol Hydrochloride	Hubei Kelun Pharmaceutical (F231206B)	NS	0.3	C
Amifostine	Nanjing Luye Cisco Pharmaceutical (23050210)	NS	1.2	C
Amikacin Sulfate	Shanghai Xinyi Jinzhu Pharmaceutical (2331102)	NS	6	C
Aztreonam	North China Pharmaceutical Group (21230604)	NS	5	C
Biapenem	Qilu Pharmaceutical (3010JFFCPA)	NS	6	C
Cefazolin Sodium	Zhejiang Huarun Sanjiu Pharmaceutical (JX2305641)	NS	10	C
Cefminox Sodium	Shantou Meiji Medicine Co., LTD (23113901)	NS	10	C
Cefoperazone Sodium and Sulbactam Sodium	Hunan Kelun Pharmaceutical (E2306009)	NS	20	C
Cefoxitin Sodium	North China Pharmaceutical Group (ETY530804)	NS	10	C
Ceftazidime	Shenzhen China Resources Jiuxin Pharmaceutical (2303238)	NS	20	C
Ceftizoxime Sodium	Suzhou Second Leaf Pharmaceutical (Z2230701)	D5W	20	C
Ceftriaxone Sodium	Hunan Kelun Pharmaceutical (E2310013)	NS	20	C
Cefuroxime Sodium	Guangzhou Baiyun Mountain Tianxin pharmaceutical (231193)	NS	15	C
Cimetidine	Shandong Lukang Pharmaceutical Group (23110801)	NS	0.8	C
Clindamycin Hydrochloride	Shandong Fangming Pharmaceutical Group (23051871)	NS	3	C
Dexamethasone Sodium Phosphate	Chenxin Pharmaceutical (N2307111)	NS	0.1	C
Diprophylline	Shanghai Modern Hasen Pharmaceutical (2304090111)	D5W	5	C
Doxofylline	Yangtze River Pharmaceutical (23080861)	NS	3	C
Esomeprazole Sodium	Hubei People's Pharmaceutical (23102111)	NS	0.4	C
Extract of Ginkgo Biloba	Yuekang Pharmaceutical Group (19830629)	D5W	0.35	C
Fosfomycin Sodium	Northeast Pharmaceutical Group (4230505)	NS	30	C
Gabexate Mesylate	Harbin Sanlian Pharmaceutical (2304232E1)	NS	0.2	C
Glutathione	Shandong Luoxin Pharmaceutical Group (523092143)	NS	18	C
Hydrocortisone Sodium Succinate	Tianjin Biochemical Pharmaceutical (012302053)	NS	1	C
Human Granulocyte Colony Stimulating Factor	Hangzhou Jiuyuan Genetic Engineering (202302005)	NS	3.75 ug	C
Lansoprazole Sodium	Jiangsu Aosaikang Pharmaceutical (J2308031)	NS	0.3	C
Ilaprazole Sodium	Rezon Pharmaceutical (230102B)	NS	0.1	C
Imipenem and Cilastatin Sodium	Merck Sharp& Dohme LLC (X028039)	NS	10	C
Magnesium Isoglycyrrhizinate	Zhengda Tianqing Pharmaceutical Group (230816104)	D5W	1	C
Meropenem	North China Pharmaceutical Group (62231011)	NS	20	C
Methylprednisolone Sodium Succinate	Rongsheng Pharmaceutical (24011805)	NS	1	C
Mycophenolate	Shuanghe Pharmaceutical	D5W	6	C
Omeprazole Sodium	North China Pharmaceutical Group (2BND231222)	NS	0.4	C
Ondansetron Hydrochloride	Harbin Sanlian Pharmaceutical (2202211L)	NS	0.08	C
Pantoprazole Sodium	Hangzhou Sino-US East China Pharmaceutical (23102111)	NS	0.4	C
Rabeprazole Sodium	Jiangsu Aosaikang Pharmaceutical (J2303042)	NS	0.2	C
Recombinant Human Interleukin-2	Beijing Sihuan Bio-pharmaceutical (20200102)	NS	20000 U	C
Tigecycline	Yangtze River Pharmaceutical (23060621)	NS	0.5	C
Tropisetron Hydrochloride	Hangzhou Minsheng Pharmaceutical (2304271)	NS	0.05	C
Tolasemil	Nanjing Youke Pharmaceutical (20230910)	NS	0.2	C
Vancomycin Hydrochloride	Eli Lilly Pharmaceutical Co (236810A)	NS	4	C
Vidarabine Monophosphate	Sinopharm One heart Pharmaceutical (2312212)	NS	2	C
Voriconazole	Lizon Group Lizon Pharmaceutical (F231103)	NS	2	C
Xuebijing	Tianjin Hongri Pharmaceutical (2302061)	NS	0.33 mL	C

(*Continued*)

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Table 1 (Continued).

Drug	Manufacturer (Lot)	Diluent	Concentration (mg/mL)	P/C
Xuebijing	Tianjin Hongri Pharmaceutical (2302061)	D5W	0.33 mL	C
Etoposide	Qilu Pharmaceutical (BB1K2048)	NS	0.25	C
NS	Fengyuan Pharmaceutical (3122090602)	-	-	-
D5W	Fengyuan Pharmaceutical (3122090602)	-	-	-

Abbreviations: P/C, Physicochemical compatibility; C, Compatibility; I, Incompatible; D5W, Glucose 5% w/v; NS, Normal saline/sodium chloride 0.9% w/v.

Tyndall Beam Assessment

The Tyndall effect was determined using high-intensity monodirectional light (Tyndall beam) (650 nm, 5 mw, Shenzhen Zhonglai Technology Co., LTD) at a 90° angle in front of a black background in a dark room. Any sample prevented the light from passing through the solutions,[22,23] and the Tyndall beam was considered incompatible at 0, 1, 2, and 4 h intervals.

pH Assessment

The pH value is a highly critical parameter for the stability of injectable drugs, and the change in pH value may have a significant impact on the stability of the drug solution.[24] After mixing for 0, 1, 2, and 4 h, the pH of each test solution was measured using a pH meter (Qiwei Instrument Co., Ltd, Hangzhou), according to the 2020 edition of the Pharmacopoeia of the People's Republic of China (Part IV 0631 pH Measurement Method).[25] Any combination with a change in pH of >10% compared with time-0 (immediately after mixing) was considered incompatible.[26]

Turbidity Assessments

The turbidity of each sample was measured using a laboratory-grade turbidimeter (INESA Physico Optical Instrument Co., Ltd., Shanghai, China) according to the manufacturer's recommendations. The original storage tube was gently inverted, and measurements were performed for samples at 0, 1, 2, and 4 h after mixing. Any combination that exhibited change (increase or decrease) in measured turbidity of ≥0.5 nephelometric turbidity unit (NTU) compared with time-0 (immediately after mixing) was considered incompatible.[14,27]

Spectroscopic Assessments

Spectroscopic measurements were performed using an ultraviolet visible spectrophotometer (8453 hewlett Packard diode array ultraviolet) to detect any indications of color change (A_{420nm}) or haze (A_{550nm}) over a 4-hour period. Admixtures of the carrier solutions were used as references. Admixtures were considered incompatible if the absorption varied by $A_{420\ nm}$>0.0400 or $A_{550\ nm}$ >0.0100 compared to the baseline (immediately after mixing).[24,28]

Particles Assessments

In line with Part 4 of the Chinese Pharmacopoeia (Ch.P) 2020 edition of the Chinese Pharmacopoeia, the determination of particles for infusions was conducted using the GWF-8JA Particle Counter (Tianjin Tianhe Analysis Instrument Co., Ltd., Tianjin). The compatible solutions were analyzed at certain time intervals (0, 1, 2, 4 hours) after mixing, testing a volume of at least 20 mL, analyzing four samples of 5 mL, and rejecting the results of the first sample. According to Ch.P, the amount of particles in solution is considered compatible if it is less than 3 particles mL^{-1} measuring 25 μm and less than 25 particles mL^{-1} measuring 10 μm.[21]

Definition of Compatibility

In this study, compatibility was defined as physical and chemical compatibility (appearance, turbidity, particle formation, pH value, and Spectroscopic): Compared with 0 h, the mixture in the 4-hour period with no color changes, no gas evolution, particulate formation, and no Tyndall beam detected in the visual examination, turbidity changes <0.5 NTU,

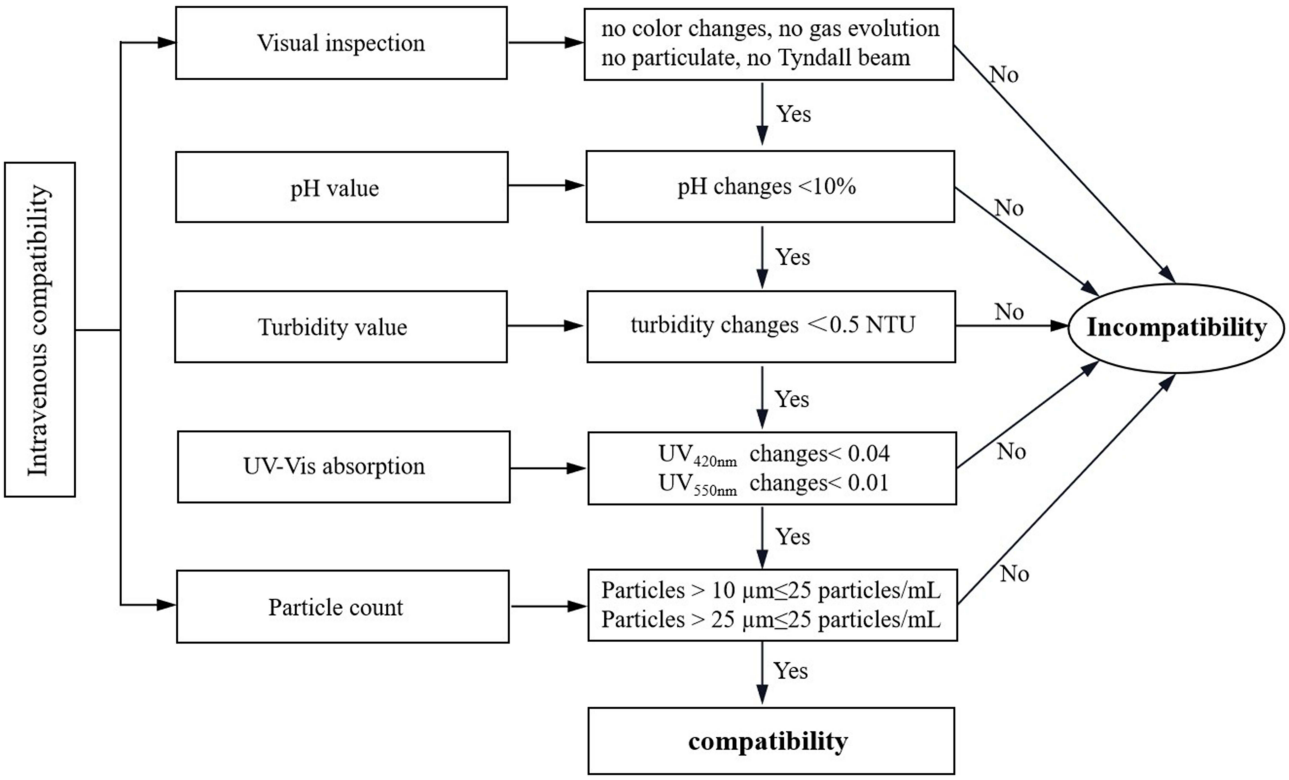

Figure 1 Diagram of compatibility justification.

particle limits allowed over the ChP, pH changes <10%, absorption changes by $A_{420\ nm} < 0.0400$ or $A_{550\ nm} < 0.0100$.[14,21–28] The justification for compatibility is shown in Figure 1.

Statistical Analysis

Descriptive statistics and original data were presented. All experiments are performed three times and expressed by means of average values. Results of particle count were reported as mean ± standard deviations (mean ± SD). No further statistical analysis was performed.

Result

Visual Inspection and Tyndall Beam Findings

Visual examinations showed that most of the drugs tested were compatible (n= 45) with etoposide, and there were no color changes, gas evolution, haze, or visible particulate formation over the time period of 4 h. Only combinations of etoposide with ilaprazole sodium were light green in 10 min, and then gradually turned dark green over 4 h. The results are shown in Figure 2.

All combinations passed the Tyndall beam tests. As shown in Figure 3, the combination of etoposide + ceftazidime, etoposide + cefuroxime sodium, etoposide + glutathione, etoposide + ilaprazole, etoposide + mycophenolate blocked the passage of light through the tube displaying the Tyndall Beam, indicating that these solutions were incompatible.

pH and Turbidity Changes Findings

To assess whether an acid–base reaction might be responsible for any observed incompatibilities, pH measurements were performed. The results in Figure 4 show that the pH values of all combinations changed by no more than 10% within 4 h, except for the combination of etoposide and cefuroxime sodium, which displayed a major change in the pH value after 4 h of incubation. Furthermore, the pH value of etoposide + cefuroxime sodium changed from at baseline 4.88 further increased to 5.55, with an overall mean change of 0.67 (13.66%). Therefore, Cefuroxime sodium was deemed incompatible with etoposide, based on this change in pH.

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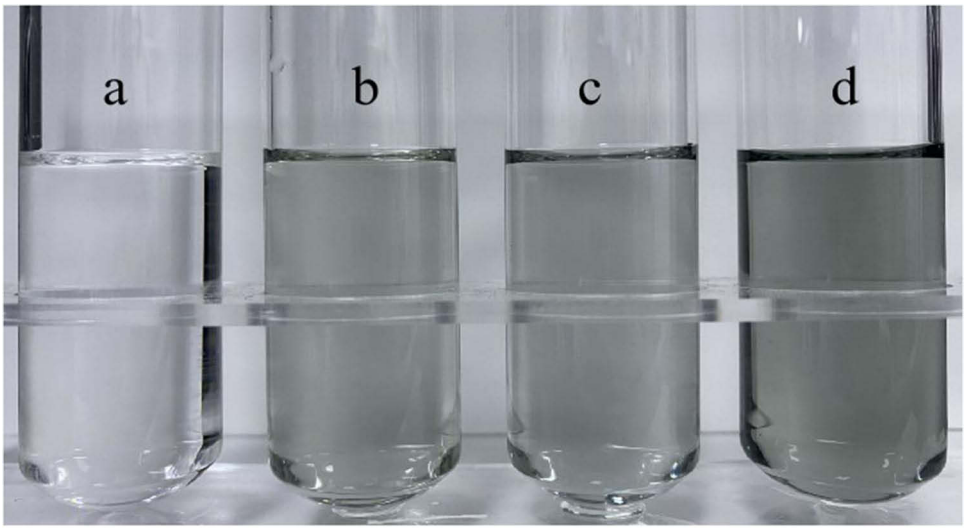

Figure 2 Visual inspection (color changes) of combinations of etoposide + ilaprazole sodium. (**a**) Negative control, etoposide + ilaprazole sodium in NS at 0 h; (**b**) Combination of etoposide + ilaprazole sodium in NS at 10 min, the color changed to light green; (**c**) Combination of etoposide + ilaprazole sodium in NS at 1 h, the color changed to blue-green; (**d**) Combination of etoposide + ilaprazole sodium in NS at 4 h; the color changed to dark green.

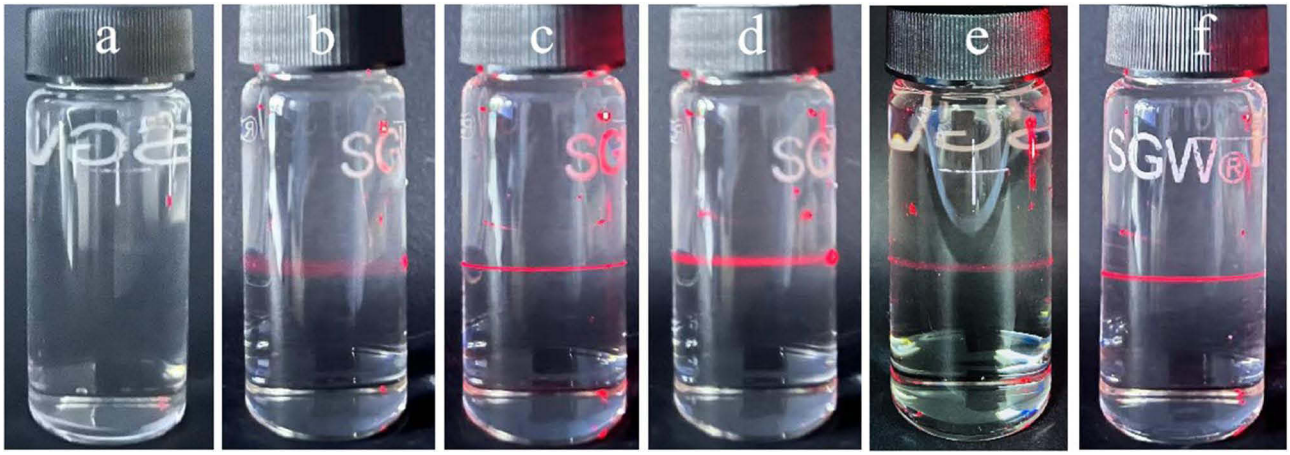

Figure 3 Tyndall beam of solutions. (**a**) Negative control, etoposide in NS; (**b**) Combination of etoposide + ceftazidime in NS at 4 h; (**c**) Combination of etoposide + cefuroxime sodium in NS at 1 h; (**d**) Combination of etoposide + glutathione in NS at 0 h; (**e**) Combination of etoposide + ilaprazole sodium in NS at 1 h; (**f**) Combination of etoposide + mycophenolate in D5W at 1 h.

The most common observation of incompatibility was a change in turbidity, and any combination with a mean increase in nephelometric turbidity units of >0.5, compared to 0 h, was considered incompatible.[29,30] As shown in Figure 4, turbidity measurements indicated that among the 45 selected drugs, combinations of etoposide +44 drugs resulted in turbidity changes of <0.5 NTU at any time point. Notably, compared with the 0 h treatment, the turbidity changes of the combinations of etoposide and mycophenolate were significantly increased, and turbidity changes were >0.5 NTU, suggesting that etoposide was incompatible with mycophenolate.

Particle Count Findings

To determine whether the drug mixture was compatible, the number of particles ≥10μm and ≥25μm in size were counted. The particles measurement demonstrated that combination of etoposide and ceftazidime displayed an increased quantity of particles not within the specifications after 4 h, combinations of etoposide + glutathione and etoposide + human granulocyte colony stimulating factor displayed massive growth in number of particles not within the specifications

Drug	pH Immediately	pH Change(%)			Turbidity Immediately After Mixing	Turbidity Change(NTU)			P/C
		1 h	2 h	4 h		1 h	2 h	4 h	
Aciclovir Sodium	9.26	0.49%	0.49%	0.19%	0.062	0.020	0.024	0.017	C
Ambroxol Hydrochloride	4.55	3.59%	3.08%	2.20%	0.061	0.020	0.020	0.011	C
Amifostine	6.39	0.94%	3.29%	1.88%	0.188	0.004	0.001	0.003	C
Amikacin Sulfate	5.18	0.32%	0.32%	0.32%	0.059	-0.007	-0.011	-0.002	C
Aztreonam	5.18	0.77%	1.16%	1.35%	0.178	-0.007	-0.019	-0.008	C
Biapenem	4.62	0.87%	1.95%	0.00%	0.145	0.007	0.008	0.007	C
Cefazolin Sodium	4.48	0.67%	0.45%	1.12%	0.104	-0.008	-0.008	-0.021	C
Cefminox Sodium	5.36	0.54%	0.65%	0.47%	0.097	0.021	0.018	0.026	C
Cefoperazone Sodium and Sulbactam Sodium	4.40	0.45%	0.91%	0.45%	0.291	-0.022	-0.015	-0.018	C
Cefoxitin Sodium	4.36	0.23%	0.92%	3.21%	0.078	0.001	0.005	-0.003	C
Ceftazidime	6.33	0.47%	0.42%	3.90%	0.070	0.006	0.003	0.005	C
Ceftizoxime Sodium	5.56	0.54%	0.54%	1.08%	0.453	-0.024	-0.012	-0.011	C
Ceftriaxone Sodium	6.00	0.17%	0.17%	0.17%	0.116	-0.004	0.000	0.002	C
Cefuroxime Sodium	4.88	2.12%	7.45%	13.66%	0.118	0.003	-0.007	-0.012	I
Cimetidine	5.23	0.25%	0.89%	1.02%	0.076	0.006	0.003	0.015	C
Clindamycin Hydrochloride	6.57	0.15%	0.76%	0.20%	0.068	0.010	0.000	0.002	C
Dexamethasone Sodium Phosphate	5.48	1.09%	1.58%	1.70%	0.115	0.002	0.003	0.001	C
Diprophylline	4.52	0.49%	0.49%	1.23%	0.090	-0.003	0.002	0.003	C
Doxofylline	4.18	0.96%	0.72%	1.20%	0.071	-0.006	-0.001	-0.002	C
Esomeprazole Sodium	8.93	0.08%	0.79%	1.21%	0.147	-0.040	-0.058	-0.008	C
Extract of Ginkgo Biloba	5.78	0.58%	0.58%	0.52%	0.048	-0.011	-0.005	-0.006	C
Fosfomycin Sodium	7.65	0.00%	0.00%	0.13%	0.158	-0.003	-0.017	-0.018	C
Gabexate Mesylate	4.21	0.71%	1.03%	1.43%	0.037	0.006	0.002	0.004	C
Glutathione	5.03	0.27%	0.33%	0.00%	0.215	-0.038	-0.037	-0.028	C
Hydrocortisone Sodium Succinate	6.07	0.38%	0.22%	0.22%	0.097	0.009	0.016	0.02	C
Human Granulocyte Colony Stimulating Factor	4.12	0.97%	1.37%	0.97%	0.115	-0.001	0.017	0.028	C
Iansoprazole Sodium	9.09	0.33%	0.11%	0.07%	0.064	-0.006	-0.005	0.024	C
Ilaprazole Sodium	6.50	3.38%	6.12%	8.15%	0.120	0.020	0.044	0.019	C
Imipenem and Cilastatin Sodium	7.06	0.09%	0.14%	0.14%	0.277	-0.002	-0.009	-0.02	C
Magnesium Isoglycyrrhizinate	4.90	6.67%	5.71%	6.26%	0.093	-0.003	-0.027	-0.017	C
Meropenem	7.96	0.13%	0.38%	0.50%	0.235	0.002	-0.003	-0.02	C
Methylprednisolone Sodium Succinate	7.09	0.89%	0.47%	0.28%	0.169	-0.021	0.015	-0.03	C
Mycophenloate	6.37	0.12%	0.27%	0.17%	0.357	0.581	0.626	0.713	I
Omeprazole Sodium	8.88	0.23%	0.00%	0.45%	0.121	0.008	0.020	0.021	C
Ondansetron Hydrochloride	4.13	0.48%	1.05%	0.81%	0.099	-0.002	0.015	-0.003	C
Pantoprazole Sodium	8.23	0.28%	0.61%	0.61%	0.149	-0.013	-0.001	0.003	C
Rabeprazole Sodium	7.69	2.08%	0.26%	0.35%	0.119	-0.023	-0.031	0.007	C
Recombinant Human Interleukin-2	4.21	1.90%	0.24%	0.24%	0.071	0.007	0.004	0.008	C
Tigecycline	4.85	0.62%	0.69%	0.55%	0.060	-0.007	-0.011	-0.024	C
Tropisetron Hydrochloride	4.37	0.53%	1.60%	1.37%	0.120	-0.035	-0.016	-0.015	C
Tolasemil	8.22	0.12%	0.24%	0.12%	0.054	0.021	0.014	0.008	C
Vancomycin Hydrochloride	4.79	0.76%	0.81%	0.79%	0.077	0.011	0.009	0.017	C
Vidarabine Monophosphate	6.83	0.29%	0.15%	0.29%	0.482	-0.002	-0.004	0.001	C
Voriconazole	6.14	0.19%	0.11%	0.18%	0.056	0.009	-0.007	0.005	C
Xuebijing	5.23	0.28%	0.17%	0.16%	0.117	0.012	0.009	0.011	C

Figure 4 The results at each time point are expressed as the average value, n=3; The pH and turbidity changes of mixture of etoposide with other medication in ratio 1: 1. Compared to 0 h, compatibility was defined as pH changes < 10%, turbidity changes < 0.5 NTU.
Abbreviations: P/C, Physicochemical compatibility; C, Compatible; I, Incompatible.

immediately after admixture, combinations of etoposide + mycophenolate and etoposide + xuebijing developed increased significantly particles count after 1 h and exceed the limitation of the specifications (Table 2). These results revealed that etoposide is incompatible with the five drugs mentioned above.

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Table 2 The Particle Count of Mixture of Etoposide with Other Medication in Ratio 1:1

Drug	≥10 μm Particles/mL				≥25 μm Particles/mL				P/C
	0	1	2	4	0	1	2	4	
Aciclovir Sodium	4.1±0.2	12.3±0.3	5.8±0.2	8.9±0.2	0.3±0.0	0.2±0.1	0.1±0.0	0.3±0.1	C
Ambroxol Hydrochloride	6.8±0.4	9.3±0.2	8.8±0.1	7.7±0.3	0.3±0.1	0.3±0.1	1.5±0.1	0.1±0.0	C
Amifostine	3.8±0.0	2.4±0.1	7.1±0.2	6.3±0.1	0.0±0.0	0.0±0.0	0.6±0.1	0.2±0.1	C
Amikacin Sulfate	2.4±0.2	5.8±0.2	3.2±0.1	4.1±0.2	0.0±0.0	0.3±0.1	0.1±0.0	0.4±0.1	C
Aztreonam	5.9±0.5	5.5±0.4	4.6±0.5	7.2±0.7	0.1±0.0	0.2±0.1	0.3±0.0	0.3±0.1	C
Biapenem	9.7±0.7	18.2±0.4	13.6±0.4	15.2±0.5	0.2±0.0	0.4±0.1	0.1±0.0	0.4±0.1	C
Cefazolin Sodium	10.5±0.6	7.1±0.7	10.2±0.4	7.9±0.5	0.3±0.0	0.2±0.1	0.3±0.1	0.3±0.0	C
Cefminox Sodium	19.0±1.7	19.3±1.9	20.1±2.1	18.3±1.3	0.9±0.2	1.7±0.3	1.9±0.3	1.3±0.2	C
Cefoperazone Sodium and Sulbactam Sodium	21.1±3.8	14.7±2.4	12.4±1.6	12.7±1.9	1.0±0.3	0.5±0.2	0.0±0.0	0.3±0.1	C
Cefoxitin Sodium	8.4±1.1	16.7±3.1	13.8±2.3	15.6±1.8	0.5±0.2	0.7±0.2	0.2±0.0	0.9±0.3	C
Ceftazidime	9.9±1.1	10.3±0.9	10.6±0.8	42.3±6.6	0.7±0.1	0.3±0.1	0.8±0.2	1.6±0.6	I
Ceftizoxime Sodium	13.3±1.0	10.9±1.4	8.9±1.1	11.9±0.6	0.3±0.1	0.3±0.0	0.3±0.0	2.3±0.9	C
Ceftriaxone Sodium	6.8±0.5	6.4±1.1	4.4±0.8	5.1±0.5	0.3±0.0	0.1±0.0	0.1±0.0	0.6±0.2	C
Cefuroxime Sodium	13.3±2.9	11.8±1.8	8.8±0.9	8.3±1.0	0.7±0.3	0.3±0.0	0.2±0.1	0.1±0.0	C
Cimetidine	4.5±0.5	6.2±0.7	5.7±0.2	4.8±0.7	0.1±0.0	0.2±0.1	0.5±0.1	0.3±0.1	C
Clindamycin Hydrochloride	4.7±0.2	5.6 ±1.1	6.9±1.7	6.9±1.3	0.1±0.0	0.2 ±0.0	0.1 ±0.1	0.1±0.0	C
Dexamethasone Sodium Phosphate	6.3±1.2	5.7±1.0	5.3±0.5	5.2±1.4	0.2±0.0	0.4±0.2	0.6±0.2	0.4 ±0.2	C
Diprophylline	3.2 ±1.1	4.7±1.0	4.8±0.7	2.9±0.5	0.4±0.1	0.2±0.0	0.2±0.0	0.7±0.2	C
Doxofylline	21.2±1.7	15.3±3.4	14.9±1.2	12.9±2.2	0.7±0.1	0.3±0.1	0.3±0.0	0.2±0.0	C
Esomeprazole Sodium	19.4±1.9	17.6±2.0	18.5±2.1	17.3±1.3	0.6±0.1	0.9±0.4	2.0±0.3	1.3±0.2	C
Extract of Ginkgo Biloba	13.8±1.5	13.8±1.7	17.7±2.2	14.2±0.8	0.0±0.0	0.2±0.1	0.3±0.0	0.3±0.1	C
Fosfomycin Sodium	12.1±0.5	13.9±1.1	9.0 ±0.6	10.1±1.1	0.1±0.0	0.8±0.2	0.1±0.0	0.1±0.0	C
Gabexate Mesylate	12.2±0.7	14.5±1.3	14.4±1.7	13.1±0.9	0.1±0.0	0.4±0.1	0.2±0.0	0.1±0.0	C
Glutathione	180.5±43.4	125.1±33.1	111.6±26.5	115.4±27.4	16.6±4.4	10.0±2.7	10.3±1.5	10.6±1.6	I
Hydrocortisone Sodium Succinate	14.6±1.4	14.0±1.1	10.3±1.3	16.0±2.1	0.4±0.2	0.4±0.2	0.3±0.1	1.1±0.7	C
Human Granulocyte Colony Stimulating Factor	35.6±9.3	12.9±2.4	20.2±3.3	32.4±7.6	2.6±1.4	1.2±0.8	1.4±0.6	4.0±1.0	I
Lansoprazole Sodium	7.5±1.2	7.8±0.6	16.9±1.6	16.5±1.3	0.3±0.2	0.5±0.2	1.0±0.5	0.5±0.2	C
Ilaprazole Sodium	8.1±0.5	22.1±1.1	10.5±0.7	12.5±1.0	0.3±0.1	0.4±0.2	0.3±0.1	0.6±0.3	C
Imipenem and Cilastatin Sodium	9.8±1.9	10.3±2.1	8.7±1.6	9.9±1.2	0.9±0.1	0.5±0.3	0.2±0.1	0.6±0.2	C
Magnesium Isoglycyrrhizinate	23.1±1.1	18.9±1.3	23.6±1.2	22.0±1.7	0.4±0.2	0.4±0.2	0.8±0.4	1.1±0.3	C
Meropenem	15.8±1.2	15.2±3.4	12.1±2.3	7.4±1.6	0.0 ±0.0	0.5±0.2	1.0 ±0.3	0.4±0.2	C
Methylprednisolone Sodium Succinate	17.9±2.3	12.6±1.5	15.3±2.7	10.0±1.8	0.6±0.3	0.2±0.1	1.0±0.4	0.6±0.3	C
Mycophenolate	17.6±7.7	27.5±9.2	39.3±8.4	37.2±8.1	3.1±1.1	3.5±1.2	4.7±0.7	4.3±2.1	I
Omeprazole Sodium	8.7±1.5	7.6 ±1.4	13.5±2.8	9.3±1.9	0.1±0.0	0.3±0.2	0.7±0.4	0.4±0.2	C
Ondansetron Hydrochloride	4.8±1.1	3.7±0.8	3.4±1.5	5.3±1.7	0.1±0.0	0.4±0.2	0.0±0.0	0.1±0.1	C

Pantoprazole Sodium	14.0±0.5	17.3±1.9	12.5±1.1	15.5±2.2	0.1±0.0	0.7±0.3	0.3±0.2	0.5±0.1	C
Rabeprazole Sodium	21.9±1.6	16.7±2.4	21.9±2.8	22.1±3.3	0.7 ±0.5	1.0±0.7	0.3 ±0.1	1.3±0.6	C
Recombinant Human Interleukin-2	10.7±1.9	6.1±2.9	21.0±2.7	20.5±2.5	1.3±1.1	0.2±0.1	0.6±0.2	0.8±0.3	C
Tigecycline	4.5±1.0	3.9±1.1	6.0±1.5	2.8±1.4	0.2±0.1	0.3 ±0.1	0.6±0.3	0.1±0.0	C
Tropisetron Hydrochloride	3.1±1.0	3.1±1.9	3.0±0.3	3.9±1.1	0.2 ±0.1	0.1 ±0.1	0.3±0.2	0.3±0.0	C
Tolasemil	10.4±1.8	8.7±1.4	9.6±2.2	11.3±3.3	0.2 ±0.1	0.0±0.0	0.5±0.4	0.3±0.1	C
Vancomycin Hydrochloride	13.2±4.7	14.1±4.9	17.7±3.6	16.4±3.8	0.8±0.4	0.7±0.5	0.8±0.4	0.6±0.2	C
Vidarabine Monophosphate	16.5±3.9	14.6±3.2	13.7±1.6	11.7±2.3	0.4 ±0.3	0.5±0.2	0.0 ±0.0	0.5±0.2	C
Voriconazole	17.2±2.0	16.5±3.1	15.4±1.6	21.9±1.4	1.5±0.2	1.2±0.2	1.0±0.1	1.8±0.3	C
Xuebijing	23.9±3.9	26.7±4.2	29.3±4.6	32.1±5.7	1.7±0.3	3.0±0.4	4.3±0.7	4.7 ±0.7	I

Notes: The variation is presented as SD at each time point, n = 3; According to Ch.P, the average number of subvisible particles is ≤ 25 per container for particle sizes ≥10 μm and ≤ 3 per container for particle sizes ≥ 25μm;
Abbreviations: P/C, Physicochemical compatibility; C, Compatibility; I: Incompatible.

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Photometrical Changes Findings

All test admixtures with absorption at 420 and 550 nm were detected, and etoposide appeared to be compatible with the majority of the drugs tested, except for ilaprazole (Figure 5). The results showed that binary combinations of etoposide with ilaprazole sodium displayed A_{420nm} changes (0.0671) > 0.0400 and A_{550nm} changes (0.0330) > 0.0100 after 1 h. Shockingly, the A_{420nm} and A_{550nm} value changes of combinations of etoposide with ilaprazole sodium increased by approximately 367.5% and mostly by 230%, respectively, after 4 h.

Discussion

Etoposide is a popular anticancer drug that inhibits topoisomerase II and is widely used in combination with other drugs to treat many critical tumors,[31] which may interact with other medications in the Y-site connector within minutes, potentially inducing physicochemical incompatibility. This is the first study of the physicochemical compatibility of etoposide with others continuous infusion drugs commonly administered in Tumour Critical Care Units. The etoposide formulation diluted with 0.9% sodium chloride was a clear, colorless, free-flowing solution under ambient light. Therefore, the changes in the solution, including gas, color, turbidity, and particles, were incompatible.

For safe Y-site administration of drug combinations, physicochemical degradation of components during Y-site administration is not a concern because of the short contact time. However, the combination of drugs and menstruum has the potential for physical and chemical reactions, based on pharmaceutical formulation principles. The calculated in-line contact time between drugs at the Y-site is at most 4 h,[14,31] and for this reason, the study time for the majority of Y-site compatibility studies was established as 4 h. In this study, we evaluated the physicochemical compatibility of etoposide with 45 selected intravenous drug combinations within 4 hours. The results showed that seven drugs were compatible with etoposide for Y-site administration, which is of great significance in clinical practice.

Ilaprazole is a sodium salt with very low solubility in aqueous solution; therefore, it can induce immediate discoloration when in contact with etoposide acid solution. The results showed that ilaprazole sodium incompatibility with etoposide immediately appeared light green after 10 min and gradually turned dark green after 4 h. Koller et al[24] reported that colorless, nearly colorless, or light-colored drug solutions were considered incompatible if the absorption varied by more than 0.0400 units at 420 nm or by 0.0100 units at 550 nm. Consistently, we showed similar results: binary combinations of etoposide with ilaprazole sodium displayed A_{420nm} changes > 0.0400 and A_{550nm} changes > 0.0100. Meanwhile, the Combination of etoposide + ilaprazole sodium in NS produced a Tyndall Beam at 1 h. As a control index of solution properties for intravenous drugs, the Tyndall effect can directly reflect the solution quality and compatibility of intravenous drugs without damaging the package of drug solutions.[22,32] Based on these results, we demonstrated that the combination of etoposide + ceftazidime, etoposide + cefuroxime sodium, etoposide + glutathione, etoposide + ilaprazole sodium, and etoposide + mycophenolate blocked the passage of light through the tube displaying the Tyndall Beam, indicating that its visual characteristics are not compatible. In combination with theoretical considerations, static tests that enhance microprecipitation visibility using the Tyndall effect are considered a simple and sensitive compatibility assessment tool in hospital pharmacy settings.[33,34] However, our study found that the Tyndall effect observed in TPN samples seems to be an inherent property of the parenteral nutrient admixture. Notably, solutions containing fluorescent compounds can exhibit an optical axis similar to the Tyndall effect, and amino acids, which are part of TPN, can have this property.[35] The detection of this type of intravenous drug solution needs further research.

pH variation is a classical test that can be used as a simple indicator of the physical stability related to chemical reactions. The inappropriate pH of solutions will accelerate drug decomposition or precipitate.[36] Although we were unable to determine the precise cause of the incompatibilities, a slight change in the pH value over time indicated a reaction in the drug admixture.[37] Sriram S et al[38] proved that the change of pH value may drive the formation of precipitation, which is due to the formation of ionized versus un-ionized drug. More than 90% of drugs are organic, weak electrolytes, especially those compounded, manufactured, or reconstituted as injections in predominantly ionized or salt form. Consequently, acid–base reactions are the most common causes of drug incompatibility.[36] Cefuroxime is a second-generation cephalosporin antibiotic with broad antibacterial activity.[39] The structure of cefuroxime contains β-lactam and carbamoyloxymethyl moieties, which are very sensitive to pH-dependent hydrolysis in solution, easy to decompose in

Drug	0 h	A_{420nm} Change			0h	A_{550nm} Change			P/C
		1 h	2 h	4 h		1 h	2 h	4 h	
Aciclovir Sodium	0.0062	0.0011	0.0022	0.0052	0.0014	0.0021	0.0050	0.0065	C
Ambroxol Hydrochloride	0.0058	0.0037	0.0017	0.0008	0.0025	0.0027	0.0015	0.0024	C
Amifostine	0.0042	0.0055	0.0006	0.0037	0.0043	0.0015	-0.0029	-0.0002	C
Amikacin Sulfate	0.0033	0.0006	-0.0013	-0.0008	0.0030	-0.0007	-0.0030	-0.0014	C
Aztreonam	0.0031	-0.0010	0.0010	0.0008	0.0007	-0.0003	-0.0004	0.0011	C
Biapenem	0.0034	0.0008	-0.0007	0.0011	0.0009	-0.0001	-0.0009	-0.0005	C
Cefazolin Sodium	0.0049	-0.0020	-0.0017	-0.0024	0.0054	-0.0039	-0.0045	-0.0027	C
Cefminox Sodium	0.0083	0.0011	0.0012	0.0017	0.0091	0.0022	0.0018	0.0012	C
Cefoperazone Sodium and Sulbactam Sodium	0.0036	0.0007	0.0048	0.0013	0.0002	0.0006	0.0054	-0.0001	C
Cefoxitin Sodium	0.0079	-0.0009	0.0035	-0.0015	0.0024	-0.0010	0.0036	-0.0007	C
Ceftazidime	0.0065	0.0032	0.0016	0.0002	0.0007	0.0029	0.0026	-0.0006	C
Ceftizoxime Sodium	0.0095	0.0001	-0.0003	0.0022	0.0025	0.0002	-0.0010	-0.0001	C
Ceftriaxone Sodium	0.0134	0.0050	0.0081	0.0179	0.0032	0.0002	-0.0021	0.0005	C
Cefuroxime Sodium	0.0046	-0.0023	0.0026	0.0046	0.0000	0.0000	0.0000	0.0000	C
Cimetidine	0.0038	0.0005	-0.0033	-0.0012	0.0073	0.0015	-0.0037	-0.0006	C
Clindamycin Hydrochloride	0.0055	-0.0001	-0.0004	0.0103	0.0057	-0.0025	-0.0043	0.0058	C
Dexamethasone Sodium Phosphate	0.0037	-0.0013	0.0011	0.0005	0.0028	-0.0001	0.0020	0.0007	C
Diprophylline	0.0013	0.0002	0.0041	0.0037	0.0027	-0.0015	0.0038	0.0009	C
Doxofylline	0.0085	0.0011	0.0006	0.0013	0.0012	0.0009	-0.0007	0.0005	C
Esomeprazole Sodium	0.0025	-0.0025	0.0102	0.0068	0.0000	0.0000	0.0023	0.0035	C
Extract of Ginkgo Biloba	0.0450	0.0075	0.0077	0.0042	0.0000	0.0039	0.0058	0.0035	C
Fosfomycin Sodium	0.0059	-0.0014	-0.0008	-0.0017	0.0053	0.0003	-0.0018	-0.0013	C
Gabexate Mesylate	0.0042	-0.0028	0.0004	0.0025	0.0032	-0.0032	-0.0032	-0.0004	C
Glutathione	0.0039	-0.0004	0.0021	0.0000	0.0011	-0.0008	0.0042	0.0023	C
Hydrocortisone Sodium Succinate	0.0024	0.0016	0.0014	0.0002	0.0000	0.0002	0.0019	0.0005	C
Human Granulocyte Colony Stimulating Factor	0.0045	0.0012	0.0004	0.0009	0.0021	0.0012	0.0009	0.0007	C
Iansoprazole Sodium	0.0018	0.0000	0.0003	0.0037	0.0023	0.0019	0.0021	0.0053	C
Ilaprazole Sodium	0.0861	0.0671	0.1285	0.1877	0.0517	0.0330	0.0713	0.1082	I
Imipenem and Cilastatin Sodium	0.0071	0.0004	-0.0012	-0.0004	0.0030	-0.0017	-0.0023	-0.0002	C
Magnesium Isoglycyrrhizinate	0.0145	0.0032	0.0044	-0.0019	0.0071	-0.0012	0.0013	0.0027	C
Meropenem	0.0138	-0.0007	0.0014	0.0037	0.0032	-0.0026	-0.0005	0.0015	C
Methylprednisolone Sodium Succinate	0.0010	0.0021	0.0015	-0.0010	0.0024	0.0018	0.0017	-0.0024	C
Mycophenloate	0.0096	0.0012	0.0017	-0.0007	0.0052	0.0032	0.0017	0.0028	C
Omeprazole Sodium	0.0037	0.0224	0.0146	0.0056	0.0015	0.0013	0.0042	0.0028	C
Ondansetron Hydrochloride	0.0038	-0.0009	0.0041	-0.0007	0.0062	-0.0049	-0.0005	-0.0012	C
Pantoprazole Sodium	0.0021	-0.0021	0.0125	0.0044	0.0012	-0.0012	0.0037	0.0010	C
Rabeprazole Sodium	0.0115	0.0063	0.0108	0.0171	0.0044	0.0000	0.0036	0.0008	C
Recombinant Human Interleukin-2	0.0040	-0.0009	0.0018	-0.0008	0.0062	-0.0007	0.0010	-0.0010	C
Tigecycline	0.8005	0.0061	0.0005	-0.0036	0.0024	0.0040	0.0027	-0.0008	C
Tropisetron Hydrochloride	0.0047	0.0009	-0.0003	0.0019	0.0062	0.0011	0.0013	-0.0003	C
Tolasemil	0.0032	0.0050	0.0023	0.0034	0.0032	0.0012	-0.0002	0.0001	C
Vancomycin Hydrochloride	0.0076	0.0012	0.0013	0.0021	0.0088	0.0009	-0.0022	-0.0019	C
Vidarabine Monophosphate	0.0038	0.0010	0.0048	0.0024	0.0029	0.0012	0.0068	0.0039	C
Voriconazole	0.0097	0.0041	-0.0011	0.0022	0.0096	0.0021	0.0019	0.0022	C
Xuebijing	0.0877	-0.0119	0.0098	-0.0078	3.3454	0.0091	0.0097	0.0073	C

Figure 5 The results at each time point are expressed as the average value, n=3; The photometrical changes of mixture of etoposide with other medication in ratio 1: 1. Compared to 0 h, Compatibility was defined as absorption changes by $A_{420\ nm} < 0.0400$ or $A_{550\ nm} < 0.0100$.
Abbreviations: P/C, Physicochemical compatibility; C, Compatible; I, Incompatible.

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acidic or alkaline environment, and contain functional groups that are easy to oxidize.[40] In this study, all combinations were within the pH range of 4.0 to 10.0, the only medication that failed pH compatibility testing was etoposide + cefuroxime sodium, the absolute pH change after incubation for 4 h was 0.67 (13.66%), exceeding the tolerance pH change limit by 10%. Therefore, it is recommended to complete the infusion within 4 hours and avoid exposure to light and air.

Most drug incompatibilities are a manifestation of acid-base changes; therefore, pH measurements can be used to detect such incompatibilities, but mixtures should not be labeled as incompatible based solely on changes in pH.[41] Subsequently, in this investigation, pH was analyzed to predict possible incompatibilities, and their incompatibility was further detected by turbidity. The turbidity of the solutions can be determined by measuring the intensity of transmitted or scattered light. Kondo M et al[27] showed that physical incompatibility has been defined as an increase in the measured turbidity exceeding 0.5 NTU. The turbidity experiments confirmed that all combinations had turbidity values of less than 0.5 NTU, except for the combination of etoposide and mycophenolate, which may be due to the formation of hydrolysates of mycophenolate mofetil solution under the conditions of strong acid, strong alkali, high temperature and light damage.[42]

Patients with critical tumors require prolonged chemotherapy to maintain treatment and multiple-drug infusion. Due to limited intravenous access, the infusion rate of all intravenous solutions through the Y tube is reduced, which extends the contact time between the components of the mixture and easily leads to the generation of particles.[43] The United States Pharmacopoeia (USP)[44] and the European Pharmacopoeia (EP),[45] define particulate matter observed during intravenous (IV) infusions as undissolved particles from infused solutions. The physicochemical properties of particles (ie, number, size, shape, and composition) have clinical consequences for patients. Several clinical studies have suggested that particles present in infusions might lead to complications such as respiratory, kidney or hematologic dysfunctions.[46–48] Thus, for detection of visible particles, two particle sizes (10 μm and 25 μm) were examined in accordance with Chinese Pharmacopoeia (Ch.P) 2020 edition.[21] In this report, we found that the particles in combinations of etoposide + ceftazidime, etoposide + glutathione, etoposide + human granulocyte colony stimulating factor, etoposide + mycophenolate and etoposide + xuebijing exceed the limitation of the Ch.P. Excessive insoluble particle could be explained by the following: the higher concentration of drug used in this study compared with other researches; after mixing, the solvent properties changed and insoluble particles were formed; dust particles produced during the preparation of mixture; incomplete dissolution of powder.[36] Servais H et al[49] reported that β-lactam is known to be unstable in the aqueous medium (inherent fragility of the β-lactam ring), and β-lactam antibiotics are chemically and physically incompatible with many other drugs. Therefore, we suggested that etoposide should be studied in detail before being combined with β-lactam antibiotics such as ceftazidime. Sulfhydryl is a critical functional fragment of glutathione, and when glutathione is administered intravenously with other drugs, physical incompatibility can lead to undesirable interactions between the sulfhydryl group and these drugs, possibly leading to the formation or degradation of complexes.[50] Importantly, despite the physicochemical stability of etoposide mixed with multiple drugs, we recommend consulting the latest compatibility data before administering mixed intravenous drugs and avoiding the co-administration of potentially incompatible drugs in the absence of clear supporting data.

However, this study also has certain limitations. Firstly, the experiments were conducted only under controlled laboratory conditions, which may not accurately replicate clinical scenarios such as dynamic flow or patient-specific factors. Secondly, although we assessed the compatibility of 0.25 mg/mL etoposide with multiple agents, perhaps considering the variability of its infusion concentration, necessitating further research to expand and refine the data. Lastly, this study primarily focused on physicochemical compatibility without delving into drug interactions and therapeutic efficacy of the drug mixtures, areas that are crucial for future research.

Conclusion

Etoposide was physicochemically compatible with approximately 84% of the 45 clinically relevant IV drugs used in tumor critical care units that were tested in the present study. Seven drugs (ceftazidime, cefuroxime sodium, glutathione, ilaprazole, human granulocyte colony-stimulating factor, mycophenolate, and xuebijing) were incompatible with etoposide and were not co-administered via Y-site infusions (Figure 6). If co-administration is necessary and the drug is

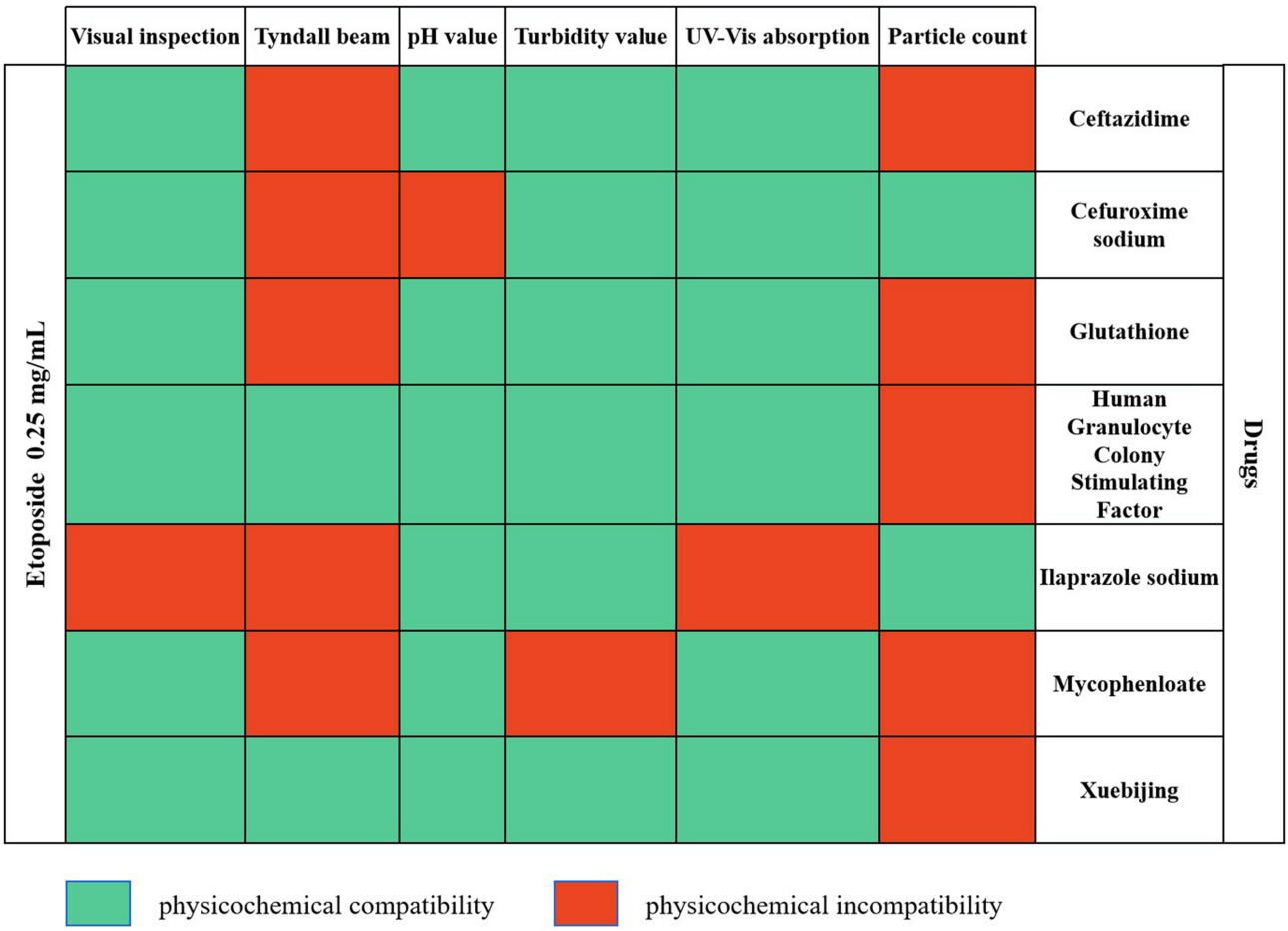

Figure 6 Incompatible of etoposide-drug pairs.

infused through a port catheter, a larger volume of saline (NS) or (D5W) should be used to flush the port catheter before and after the etoposide infusion to clean the lumen of the port catheter. Moreover, these results will contribute to an increase in Y-site compatibility data available in the literature, which will improve drug safety in tumor-intensive care, provide scientific and feasible methods for clinical intravenous drug compatibility trials.

Data Sharing Statement

The data analyzed and presented in this study are available from the corresponding author (Zhaolin Chen) on reasonable request, providing the request meets local ethical and research governance criteria after publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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