

BDMAI BULLETIN



From the Desk of President

Dear Friends,

I am pleased to connect once again with you through this edition of the BDMAI Bulletin.

The past month has been an active and productive period for the Association. During this period, BDMAI has particularly focused on regulatory matters, hazardous waste management and other operational challenges faced by the API industry.

As part of our efforts, members of the Association met the Member Secretary, Telangana Pollution Control Board, and submitted a representation requesting the Board to take a practical and balanced approach towards the requirement of installing Retrofitted Emission Control Devices (RECDs) on existing DG sets. The Association also requested the Board to closely monitor the operations and charges of hazardous waste management agencies so that member industries are not subjected to avoidable operational and financial burdens.

As we approach our Annual General Meeting, which will be held on 26th September, I look forward to the active participation of all our members. The AGM is an important occasion to review the activities and achievements of the Association, deliberate on the challenges facing the industry and collectively identify our priorities for the coming year.

We are particularly honoured that Dr. Rajeev Raghuvanshi, Drugs Controller General of India (DCGI), has kindly agreed to be the Chief Guest at the AGM. We have also invited senior officers from CDSCO and TG SAFE to grace the occasion. Their participation will provide our members with an excellent opportunity to interact

directly with senior regulatory authorities and exchange views on matters of importance to the pharmaceutical industry.

I take this opportunity to thank all our members for their continued support, confidence and active participation in the activities of BDMAI. I am confident that, through our collective efforts, the Association will continue to contribute meaningfully to the growth, competitiveness and global standing of India's bulk drug industry.

I look forward to meeting you all at the forthcoming AGM.

With warm regards,

Rameswara Rao
National President

In this Bulletin
you can expect

**Global Pharma
Market
Intelligence**

**Analysis of Bulk
Drugs Exports &
Imports (April-July)**

**Association
Activities &
Important Trade
Notifications**

Technical Article

GLOBAL PHARMA MARKET INTELLIGENCE

Executive Overview

During August/September 2026, the global pharmaceutical industry continued to show strong activity in oncology, biologics/biosimilars, peptides, rare diseases, obesity/GLP-1 therapies and complex injectable products during the period under review. An important feature of the

Major New Drug Developments & Approvals

Date	Company / Drug	Development	Therapeutic Area	Relevance to Indian API Industry
18 Aug	Rigel – Vepdegestrant (Veppanu)	US commercial launch for ER+/HER2-, ESR1-mutated advanced/metastatic breast cancer	Oncology	Opportunity for API/intermediate suppliers as the drug moves into commercialisation. Vepdegestrant is an example of the growing importance of oral targeted oncology drugs.
19 Aug	FDA – Pabinafusp? / GSD-Ia therapy	FDA approved first therapy for patients aged 8+ with Glycogen Storage Disease Type Ia	Rare disease	Rare-disease products generally involve high-value, specialised APIs and advanced manufacturing technologies. FDA listed the approval among its August 2026 approvals.
26 Aug	Revolution Medicines – Daraxonrasib (Rasonque)	FDA approved first-in-class targeted therapy for metastatic pancreatic cancer	Oncology	Particularly important for Indian API companies with capabilities in complex small molecules and oncology APIs. The drug targets RAS, a major cancer pathway.
27 Aug	Brepocitinib (Lisraya)	FDA approved first oral treatment for dermatomyositis	Immunology / Rare disease	JAK-inhibitor chemistry creates opportunities for Indian manufacturers of high-quality small-molecule APIs and intermediates.
28 Aug	Rusfertide (Mimrylo)	FDA approved first drug of its kind for polycythemia vera	Haematology	New mechanism and specialised peptide-based development highlight opportunities in high-value APIs and advanced synthesis. FDA expects significant commercial potential.
31 Aug	Ropeginterferon alfa-2b (Besremi)	FDA approved treatment for essential thrombocythemia	Haematology	Reinforces continuing demand for complex biologic/biotechnology-based drug substances.
1 Sep	IMAVVY	FDA approval as first targeted therapy for warm autoimmune haemolytic anaemia	Autoimmune / Haematology	New biologic/targeted therapies create demand for specialised drug substances, analytical services and high-quality intermediates.

GLOBAL PHARMA MARKET INTELLIGENCE

3 Sep	Zilganersen (Zanvastro)	FDA approved first drug for Alexander disease	Rare disease / CNS	Highlights the continuing shift towards highly specialised rare-disease medicines and smaller-volume, high-value APIs.
4 Sep	New breast-cancer treatment	FDA granted accelerated approval to a new breast-cancer treatment	Oncology	Oncology remains one of the strongest growth areas for complex APIs, HPAPIs and specialised intermediates.

India: Important Developments

Tapinarof – approval covering API and finished dosage

Optimus Pharma, a subsidiary of Sekhmet Pharmaventures, received DCGI permission to manufacture and market Tapinarof Cream 1% w/w and its bulk drug/API. Tapinarof is a non-steroidal topical treatment for plaque psoriasis. The development is particularly relevant to the Indian bulk-drug industry because the regulatory permission covers the bulk drug as well as the finished dosage form. Optimus is reported to be the first Indian company to obtain such approval.

CDSCO action on unapproved Enclomiphene products

On 10/11 August, CDSCO directed State and Union Territory Drug Controllers to take action against the manufacture and marketing of unapproved Enclomiphene and its combinations. CDSCO clarified that Enclomiphene qualifies as a New Drug and requires approval from the Central Licensing Authority before commercial manufacture/marketing.

Gland Pharma – major global sterile injectable CDMO contract

Gland Pharma announced a long-term Manufacturing and Supply Agreement with a global pharmaceutical company covering 55 sterile injectable SKUs across three manufacturing sites. The portfolio includes vials, lyophilised products, ampoules and pre-filled syringes. Once fully commercialised, the agreement is expected to generate approximately US\$90–100 million in annualised revenue, with commercial revenue expected from 2029.

Aurigene – manufacturing agreement for 20+ products

Aurigene Pharmaceutical Services, a subsidiary of Dr Reddy's Laboratories, entered into a strategic long-term Manufacturing and Supply Agreement with a global pharmaceutical company covering more than 20 drug products for international markets.

Lupin – European licensing deal

Lupin's subsidiary VISUfarma entered into an exclusive European licensing agreement with Visus Therapeutics for **YUVEZZI**, a treatment for presbyopia, for commercialisation across key European markets.

China: Increasingly Important Source of Innovation

China continues to move from being predominantly a manufacturing base towards becoming a significant source of innovative drug candidates and biotech assets.

Cipla – Qilu Pharmaceutical collaboration

On 3 September, Cipla announced that its US subsidiary entered into an exclusive partnership with Qilu Pharmaceutical of China for a biosimilar version of Merck's Keytruda (pembrolizumab), targeting the US market. This is strategically important because it represents Indian-Chinese cooperation in biologics/biosimilars, with the objective of entering a major regulated market.

Cipla – Sino Biopharmaceutical / CTTQ oncology deal

Cipla has also entered into an exclusive licensing and supply agreement with Chia Tai Tianqing Pharmaceutical Group (CTTQ), a subsidiary of Sino Biopharmaceutical, for TQB2102 / rolditamig deuderuxtecan, a HER2-targeted antibody-drug conjugate. Cipla will handle development, clinical trials, regulatory submissions and commercialisation in India, South Africa and other emerging markets, while CTTQ will manufacture and supply the product.

This is a significant example of Chinese-origin innovation being brought to emerging markets through an Indian pharmaceutical company.

Sandoz – Shanghai Henlius biosimilar agreement

Sandoz agreed to license three biosimilar candidates from Shanghai Henlius Biotech covering cholesterol, lupus and colorectal cancer indications. The products are biosimilars of evolocumab, belimumab and cetuximab. The agreement includes up to US\$77 million upfront, plus potential development and commercial milestones. The deal demonstrates the growing international value of China's biologics pipeline and suggests that biosimilar development will be a major source of future API/drug-substance demand.

4.4 GSK – Hutchmed licensing deal

China's Hutchmed entered into a licensing agreement with GSK for an experimental solid-tumour drug. GSK will make an upfront payment of US\$110 million, with the overall deal potentially reaching approximately US\$1.3 billion including milestones. This further confirms the emergence of China as a significant out-licensing market for innovative medicines, especially in oncology.

China expands global M&A and licensing support

Jiangsu province announced a three-year plan supporting pharmaceutical companies in global M&A, licensing and joint-development projects. China accounted for approximately 32% of global clinical trials in 2025, compared with only 2% in 2009, according to data cited in the report.

Indian API manufacturers should increasingly monitor Chinese clinical pipelines—not merely Chinese API manufacturers. Drugs entering Phase II/III development can become future opportunities for custom synthesis, intermediates, API development and commercial supply.

Latin America

Brazil – Biocon's 10-year Pertuzumab supply agreement

One of the most significant developments during the period is Biocon's agreement to supply Pertuzumab, a monoclonal antibody used in HER2-positive breast cancer, to Brazil for 10 years. The agreement involves Bahiafarma, a public pharmaceutical laboratory, and Bionovis.

Brazil is one of the largest pharmaceutical markets in Latin America and has substantial demand for affordable biological and generic medicines. The agreement demonstrates opportunities for Indian companies in Biosimilars, Monoclonal antibodies, Complex APIs, Oncology drug substances, Long-term public-sector supply arrangements, Technology transfer and local manufacturing partnerships.

Brazil and Mexico are also working on regulatory and production cooperation aimed at streamlining medical-product approvals and strengthening regional manufacturing.

Major products approaching patent expiry — 2026–2030

Expected period	Brand	API / Active Ingredient	Innovator	Main indication
2026	Eliquis	Apixaban	Bristol Myers Squibb / Pfizer	Anticoagulant
2026	Ozempic / Wegovy	Semaglutide	Novo Nordisk	Diabetes / Obesity
2026	Farxiga / Forxiga	Dapagliflozin	AstraZeneca	Diabetes / CKD / Heart failure
2026	Xtandi	Enzalutamide	Astellas / Pfizer	Prostate cancer
2027	Revlimid	Lenalidomide	Bristol Myers Squibb	Multiple myeloma
2027	Trikafta / Kaftrio	Elexacaftor + Tezacaftor + Ivacaftor	Vertex	Cystic fibrosis
2027	Ibrance	Palbociclib	Pfizer	Breast cancer
2027–28	Erleada	Apalutamide	Janssen / J&J	Prostate cancer
2028	Keytruda	Pembrolizumab	Merck & Co.	Multiple cancers
2028	Opdivo	Nivolumab	Bristol Myers Squibb	Multiple cancers
2028	Dupixent	Dupilumab	Sanofi / Regeneron	Atopic dermatitis / Asthma
2028	Entresto	Sacubitril + Valsartan	Novartis	Heart failure
2028–29	Kisqali	Ribociclib	Novartis	Breast cancer
2029	Wakix	Pitolisant	Harmony	Narcolepsy
2029	Caplyta	Lumateperone	Bristol Myers Squibb / Intra-Cellular	Schizophrenia / Bipolar disorder
2030	Ofev	Nintedanib	Boehringer Ingelheim	Pulmonary fibrosis

Note: This is not an exhaustive list.

A recent 2026 patent-cliff analysis based on FDA Orange Book data identifies 15 small-molecule blockbusters whose earliest listed US patent expires during 2026–2030, including semaglutide, dapagliflozin, enzalutamide, elexacaftor/tezacaftor/ivacaftor and lenalidomide. It separately identifies 19 biologics facing biosimilar competition.

Executive summary

Values in mn \$

Indicator	April-July 2025-26	April-July 2026- 27	Change
Bulk drug exports	1,548.79	1,688.76	+9.04%
Bulk drug imports	1,488.43	1,494.61	+0.41%
Trade balance	+60.36	+194.15	+133.79

Overall assessment

The data indicate a positive shift in India's bulk drug trade position during April–July FY-27:

- Exports increased by \$139.97 Mn, or 9.04%.
- Imports increased only \$6.18 Mn, or 0.41%.
- Consequently, the trade surplus expanded from \$60.36 Mn to \$194.15 Mn, an improvement of \$133.79 Mn.
- The export side appears relatively diversified across countries, while the import side remains extremely concentrated in China.
- On the product side, exports are led by a few large categories, while imports show significant increases in heterocyclic compounds and methionine, partially offset by declines in 6-APA and antibiotics.

Export analysis

Export Metric	April-July 2025-26	April July 2026-27	Change
Bulk drug exports	1,548.79	1,688.76	+9.04%

- A 9% increase is a reasonably strong performance, particularly when compared with the almost flat import growth.
- The increase is not uniform across products or destinations. A number of important products and markets recorded substantial growth, while some traditional products/markets declined.

Major export products

Rank	Product / HS description	2025-26	2026-27	Change %
1	Other diloxanide furoate, cimetidine, famotidine etc.	356.17	401.97	+12.86
2	Other heterocyclic compounds	239.91	258.04	+7.56
3	Other antibiotics	135.20	182.50	+34.99
4	Other of vegetable origin	57.52	58.81	+2.24
5	Amoxycillin & its salts	50.67	51.07	+0.79
6	Other steroidal hormones etc.	35.53	44.07	+24.05
7	Paracetamol	26.15	35.80	+36.88

ANALYSIS OF EXPORTS & IMPORTS OF BULK DRUGS

Rank	Product / HS description	2025-26	2026-27	Change %
8	Niacin / Niacinamide	26.20	35.62	+35.95
9	Caffeine and its salts	22.09	35.13	+59.00
10	Erythromycin & derivatives	33.76	32.15	-4.76

- The top three export categories dominate the portfolio.
- The three largest categories together account for approximately:
- \$842.51 Mn / \$1,688.76 Mn = 49.9% of total exports.
- Antibiotics were a major growth driver - Exports of "Other antibiotics" increased by approximately \$47.31 Mn, the largest absolute increase among the major export categories.
- Several products showed exceptionally strong growth. Particularly, Caffeine: +59.0% , Paracetamol: +36.9% , Niacin/Niacinamide: +36.0% , Other antibiotics: +35.0% , Steroidal hormones: +24.0%
- Amoxicillin was virtually stagnant - Exports increased only 0.79%, indicating that growth in the overall export basket is coming from other products rather than from all major traditional APIs.

Export destination analysis

Rank	Country	2025-26	2026-27	Change %
1	U.S.A.	178.51	189.91	+6.38%
2	Unspecified	107.55	119.64	+11.24%
3	Brazil	63.25	103.70	+63.96%
4	Netherlands	52.88	73.31	+38.65%
5	Bangladesh	50.89	58.70	+15.35%
6	Germany	48.27	57.64	+19.41%
7	Turkey	40.26	57.08	+41.77%
8	China	58.70	50.47	-14.03%
9	Egypt	41.24	49.76	+20.67%
10	Indonesia	34.94	40.22	+15.10%

- The U.S. remained India's largest identifiable destination: FY-26: \$178.51 Mn FY-27: \$189.91 Mn Growth: 6.38% . The U.S. accounts for approximately 11.25% of total exports, making it an important anchor market.
- Brazil is the standout growth market - Brazil increased from \$63.25 Mn to \$103.70 Mn, an increase of \$40.46 Mn / 63.96%. This is one of the most significant positive developments in the export data. Brazil alone contributed roughly 29% of the total \$139.97 Mn increase in exports.
- Netherlands and Turkey also performed strongly - Netherlands: +38.65% Turkey: +41.77% . These markets are becoming increasingly important contributors to export growth.
- China as an export destination declined - Indian exports to China fell - \$58.70 Mn → \$50.47 Mn (-14.03%) -This is notable given China's dominant position on India's import side.

Import analysis

Import metric	FY-26	FY-27	Change
Total bulk drug imports	1,488.43	1,494.61	+\$6.18 / +0.41%

The import position is essentially stable. This is strategically significant because exports grew by 9.04% while imports grew by only 0.41%.

Major imported products

Rank	Product / description	2025-26	2026-27	Change %
1	Other heterocyclic compounds	209.49	292.89	+39.81%
2	Other antibiotics	251.92	239.34	-5.00%
3	Other diloxanide furoate, cimetidine, famotidine etc.	113.56	102.52	-9.72%
4	Methionine	54.76	91.73	+67.52%
5	Erythromycin & derivatives	63.66	63.76	+0.16%
6	6-APA	117.84	58.00	-50.78%
7	Steroidal hormones etc.	35.83	50.65	+41.37%
8	Lysine and its esters/salts	40.78	44.72	+9.65%
9	Other penicillins & derivatives	29.73	28.01	-5.77%
10	Other glycosides	21.69	26.09	+20.31%

- Heterocyclic compounds are the biggest import growth driver – Imports increased from:
- \$209.49 Mn → \$292.89 Mn. An increase of \$83.39 Mn, or 39.81%.. This single category contributed more than the entire net increase in imports because other categories declined.
- Methionine imports rose sharply - Methionine increased from \$54.76 Mn → \$91.73 Mn
- or +67.52% / +\$36.97 Mn. This deserves attention as a potential area of increasing import dependence.
- 6-APA imports fell dramatically 6-APA declined from \$117.84 Mn → \$58.00 Mn. a reduction of \$59.84 Mn / 50.78%. This is one of the most important positive changes from an import-substitution perspective.
- Antibiotic imports declined "Other antibiotics" decreased by approximately \$12.59 Mn, or 5.0%.

Import source-country analysis

Rank	Country	2025-26	206-27	Change %
1	China	1,085.60	1,056.78	-2.66%
2	Italy	37.70	54.47	+44.48%
3	Singapore	31.43	42.48	+35.16%
4	Spain	28.78	36.62	+27.22%
5	Germany	38.59	29.13	-24.52%
6	U.S.A.	25.28	28.67	+13.40%
7	Japan	22.58	27.59	+22.19%
8	Switzerland	16.21	20.86	+28.68%
9	Denmark	13.06	18.79	+43.92%
10	Netherlands	19.19	16.36	-14.73%

ANALYSIS OF EXPORTS & IMPORTS OF BULK DRUGS

- China supplied approximately -\$1,056.78 Mn out of \$1,494.61 Mn or 70.71% of India's bulk drug imports in the period.
- Even though imports from China declined by 2.66%, China still represents more than 70% of total imports.

Export vs import comparison

Parameter	Exports	Imports
2025-26	1,548.79	1,488.43
2026-27	1,688.76	1,494.61
Absolute change	+139.97 mn	6.18
Growth	+9.04%	+0.41%
2026-27position	Strong growth	Almost flat
Major concentration	Product categories	China as source

Trade balance

	2025-26	2026-27
Exports	1,548.79	1,688.76
Imports	1,488.43	1,494.61
Surplus	60.36	194.15

- The surplus increased by \$133.79 Mn, or approximately 222%. This is a major improvement.
- The key reason is not that imports collapsed—they did not. Rather, exports expanded significantly while imports remained nearly unchanged.
- High-performing APIs and markets while simultaneously targeting the specific product categories responsible for import dependence.

ASSOCIATION ACTIVITIES

List of Important Circulars sent and representations made during August-September 2026

S.No.	Date	Type	Subject
1	03-08-2026	Circular	Study in E-Waste Management in Telangana by EPTRI
2	04-08-2026	Circular	Outreach Programme organized by Income Tax Department (TDS) – 6th August 2026
3	07-08-2026	Representation	Inputs to Quarterly Meeting with Stakeholders on General System Updating on Regulatory Framework and Procedures of CDSCO
4	11-08-2026	Circular	Circular Economy & Waste Recycling Policy of Andhra Pradesh Government
5	17-08-2026	Representation	Regulation of Emissions from DG Sets – Installing Retrofitted Emission Control (RECD) or shifting to gas generator
6	18-08-2026	Circular	Interactive Session with the Member Secretary, TG PCB – 20th August 2026
7	25-08-2026	Representation	Requests for a Committee in TGPCB to monitor Hazardous Waste Management Services & Online issue of CTE/CTOs in case of change in Product Mix
8	25-08-2026	Representation	Request for suitable change in name of Telangana State Authority for Food and Essential Drugs (TG SAFE)
9	03-09-2026	Circular	Clarifications sought from Re Sustainability regarding Additional Handling Charges & Surcharge

Annual General Meeting:

35th Annual General Meeting of the Association is scheduled on 26th September 2026 at Hotel Avasa, Hyderabad. Dr. Rajeev Singh Raghuvanshi, DCGI and other senior officials from CDSCO & TG-SAFE are also invited. Members are requested to make note of this important event.

INDIAN REGULATORY AND TRADE UPDATES

Important Regulatory and Trade Notifications during Aug – Sep 2026

Sl. No.	Date	Department	Notification No.	Subject
1	18.8.2026	CDSCO	S.O. 4595(E)	Restriction concerning use of specified combination in children below 4 years Chlorpheniramine Maleate + Phenylephrine HCl formulations
2	19.8.2026	CDSCO	G.S.R. 745(E)	Draft notification proposes addition of four drugs to Schedule H1
3	21.8.2026	DGFT	Trade Notice 21/2026-27	Automated Export Obligation extension – Advance Authorisation/EPCG
4	25.8.2026	DGFT	Trade Notice 22/2026-27	Changes/improvements in pre-shipment inspection processes
5	28.8.2026	DGFT	Trade Notice 23/2026-27	Digital/system-based handling of bank guarantees
6	1.9.2026	CBIC/Customs	38/2026-Customs	Implementation of Sea Cargo Manifest & Transshipment Regulations (SCMTR), 2018
7	3.9.2026	CBIC/Customs	Circular No. 39/2026-Customs	Rationalisation of documentation under Eligible Manufacturer Importer Scheme
8	3.9.2026	CBIC/Customs	Circular No. 40/2026-Customs	Checklists to be verified before Out-of-Charge; includes APIs and finished formulations
9	7.9.2026	DGFT	Trade Notice 25/2026-27	Digital/API integration with CoO system
10.	5.9.2026	CDSCO	Public Notice	Action against illegal manufacture/distribution of misbranded drugs
11	7.9.2026	DGFT	Trade Notice 26/2026-27	Proposed suspension of 544 unused SIONs. Stakeholder's comments are invited.
12	10.8.2026	CDSCO	Circular	Import/marketing permission for certain new drugs. Clarification concerning applications where Phase III GCT is ongoing/completed with Indian subjects

Deep Eutectic Solvents in Active Pharmaceutical Ingredient Development

Masataka Ito

1. Introduction

A deep eutectic solvent (DES) is a liquid obtained by mixing two solid components. DES research is attracting intense interest, particularly in DESs that are liquids over a wide temperature range because of the large melting point decrease caused by mixing hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) compounds. Since Abbott *et al.* reported DESs in 2003, DESs have been expected to find applications in various fields.¹⁾ The number of papers on DESs since 2010 has increased, with a sharp increase over the decade starting in 2015 (Fig. 1). Consequently, further expansion of applied research is anticipated.

DESs can be broadly classified into five types (Table 1). Initially, only types I–IV were recognized. However, recent reports on DESs formed with organic compounds have led to proposals for adding type V DESs, which contain HBA and HBD units and consist solely of organic compounds. For example, a DES composed of proline and sorbitol falls into this category.

Ionic liquids are similar to DESs, but the DES components do not need to be ions. A DES can be prepared using compounds that are safer than those commonly used in ionic liquids, decreasing the environmental impact of DESs. Fur

thermore, the low synthesis cost of DESs makes them suitable for various fields. For example, in DES extraction with ultrasound, the recovery efficiency of the natural pigment anthocyanin was optimized.²⁾ In catalysis, DESs prepared using quaternary ammonium salts and carboxylic acids were used as extractants for platinum group metals.³⁾

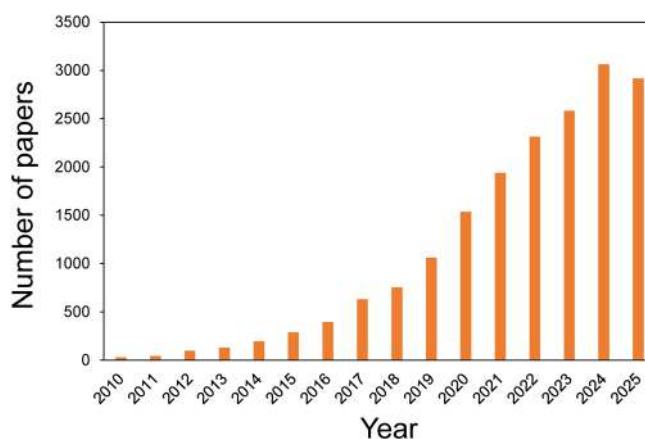


Fig. 1. Annual Trends in the Number of DES Papers

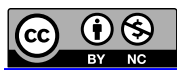


Table 1. Types of DES^{20,21)}

Type	Formula	
Type I	$\text{Cat}^+\text{X}^- + z\text{MCl}_x$	M = Zn, In, Sn, Al, Fe Cat = Cation
Type II	$\text{Cat}^+\text{X}^- + z\text{MCl}_x \cdot y\text{H}_2\text{O}$	M = Cr, Ni, Cu, Fe, Co
Type III	$\text{Cat}^+\text{X}^- + z\text{RZ}$	R = Alkyl Z = OH, COOH, CONH ₂
Type IV	$\text{MCl}_x + z\text{RZ}$	M = Zn, Al Z = OH, CONH ₂
Type V	HBA + HBD	Any organic compound capable of forming hydrogen bonds.

In pharmaceuticals, DESs have been investigated for use in drug delivery systems. A hydrophobic DES composed of menthol and decanoic acid dissolved risperidone at a concentration 7300 times higher than water and improved risperidone's skin permeability.⁴⁾ Additionally, DESs are being explored for creating slurries to obtain multicomponent crystals of active pharmaceutical ingredients (APIs).⁵⁾ However, the high viscosity and low volatility of DESs make separation of the DES from the target substance difficult. To address this, separation methods using precipitation through salting out or pH changes and the introduction of DESs recycling technology are being investigated.⁶⁾

For pharmaceutical applications of DESs, safety is a key consideration. Compounds permitted or potentially permissible for pharmaceutical use must be used to prepare the DESs, and the additive amount must consider the maximum daily allowable intake based on the target API. The Generally Recognized as Safe classification can be useful for selecting candidate compounds.

This review will explain the challenges and applications for the industrial use of DESs.

2. Viscosity of DESs

Viscosity is a key parameter of a DES, and DESs often exhibit high viscosity ($>0.1\text{ Pa}\cdot\text{s}$),⁷⁻⁹⁾ which is a challenge for industrial applications. However, DES systems where one component is liquid, such as choline chloride (ChCl)/ethylene glycol, fall below $0.1\text{ Pa}\cdot\text{s}$ near room temperature. The viscosity of DESs arises from the hydrogen bonds among their components. The many hydrogen bonds among the HBA and HBD restrict molecular freedom, reducing the fluidity of the liquid and increasing its viscosity. For example, in a DES composed of urea and ChCl (urea:ChCl = 2:1), numerous hydrogen bonds form among chloride ions and urea. The hydroxyl groups and carboxylic acids in a ChCl-based DES form extensive hydrogen bond networks, which probably restrict molecular mobility and increase viscosity. However, large ion size and small void volume are likely to be the most common factors for DESs.^{7,10)}

For a DES with the same composition, viscosity values differ among studies. The various methods for measuring liquid viscosity, such as rotational viscometer, capillary viscometer, and falling ball viscometer methods, may affect reported values. In addition, a study showed a viscosity difference of approximately 6.5% between the same DES prepared by heating and mixing methods.^{11,12)} Water content also affects viscosity and choline DESs are highly hygroscopic. The hygroscopicity can be addressed by methods such as adding water until hygroscopicity is minimized. A study reported that adding

0.1 mol of water to a ChCl/urea DES reduced its viscosity from 0.53 to $0.20\text{ Pa}\cdot\text{s}$.¹³⁾ These findings indicate that the viscosity of high-viscosity DES can be controlled by adding water.

3. Solubility of Poorly Soluble APIs

The high solubility of poorly soluble compounds in DES has been investigated for extraction. For example, the solubility of flavonoids in DES was investigated.¹⁴⁾ Similarly, poorly soluble APIs have also been examined. The solubilities of betamethasone, meloxicam, and piroxicam in a DES based on ChCl were examined and were higher than those in water.¹⁵⁾

Choline is widely used in preparing DESs, but few studies have compared choline salts other than ChCl. Therefore, the author conducted a solubility study using three DES composed of three choline salts.^{16,17)} Malonic acid (MA) and choline salts (ChCl, choline bromide (ChBr), and choline tosylate (ChTs)) were used to prepare three DESs (ChCl/MA, ChBr/MA, and ChTs/MA) (Fig. 2). The molar ratio of components in each DES was set to 1:1. The DESs were prepared by mixing solid powders in a 1:1M ratio and heating at 100°C for approximately 20 min (Fig. 2). Nine model compounds (tadalafil (TDF), piroxicam (PXC), carbamazepine (CBZ), norfloxacin (NFX), praziquantel (PZQ), cytidine (CYT), ethenzamide (EA), acyclovir (ACV), and caffeine), including poorly water-soluble APIs, were dissolved in the three DESs (Fig. 3). The model compounds were suspended in the DESs (15 mL) at 40°C , and a saturated solution was obtained after vacuum filtration. Solubility measurements were performed using HPLC. TDF, the API with the lowest water solubility of $0.66 \times 10^{-3}\text{ mg/mL}$, reached a solubility in ChTs/MA of 16.3 mg/mL , an increase of approximately 24800-fold. Solubility increases ranging from approximately 11- to 660-fold were observed for the other model compounds. The DESs dissolved poorly water-soluble APIs without organic solvents. With some exceptions, most model compounds showed solubility trends in the order ChTs/MA > ChBr/MA > ChCl/MA. In ChTs, the tosylate group contains a benzene ring, making ChTs more hydrophobic than ChBr and ChCl and increasing the solubility of model compounds in ChTs/MA compared with ChBr/MA and ChCl/MA.

4. Using DESs as the Mother Liquor for Crystallization

Salt crystals have long been used to improve the solubility of APIs, and many APIs have been developed and marketed as salt crystals. Examples include converting basic APIs into salts with mineral or organic acids, or converting acidic APIs into inorganic salts. These are compounds where the active ingredient and ion species form a stoichiometric ionic bond. Single-crystal structure analysis can reveal dissociation of dissociable groups or proton transfer, confirming the crystal formation.

The author used three DESs based on choline as the mother liquor to prepare multicomponent crystals of APIs.¹⁷⁾ Multicomponent crystallization is a widely used technique in pharmaceutical development for improving the physical properties of APIs. Multicomponent crystals include salts and cocrystals, in which API and pharmacologically acceptable components coexist in the same crystal. Generally, if proton transfer occurs, it is called a salt; if not, it is called a cocrystal.

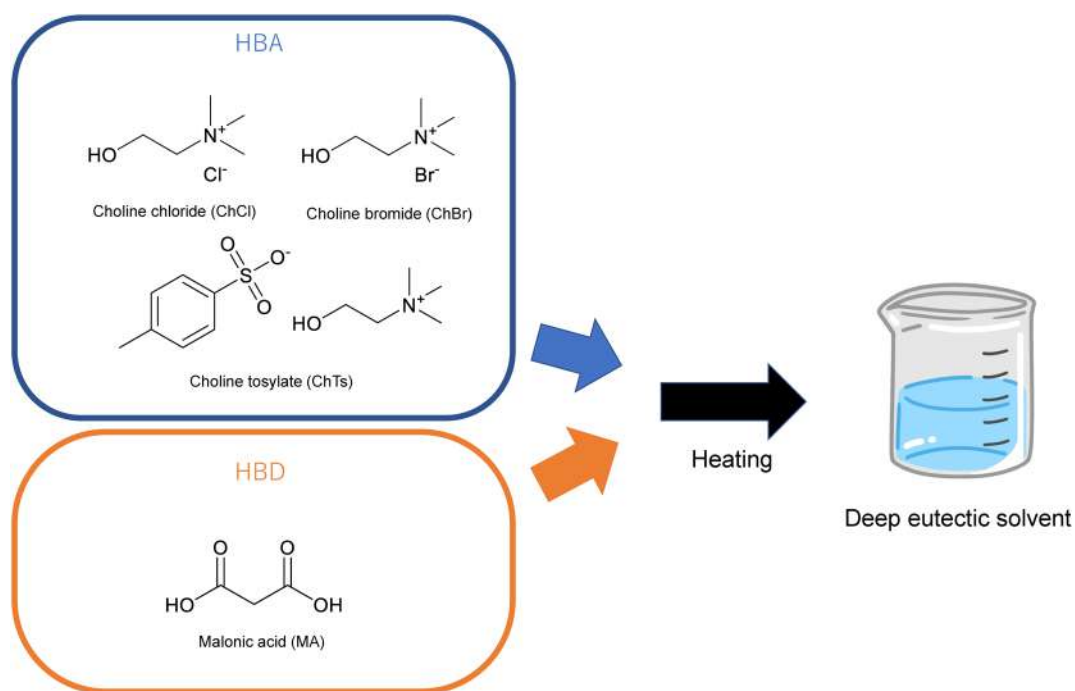


Fig. 2. Preparation Method for DESs

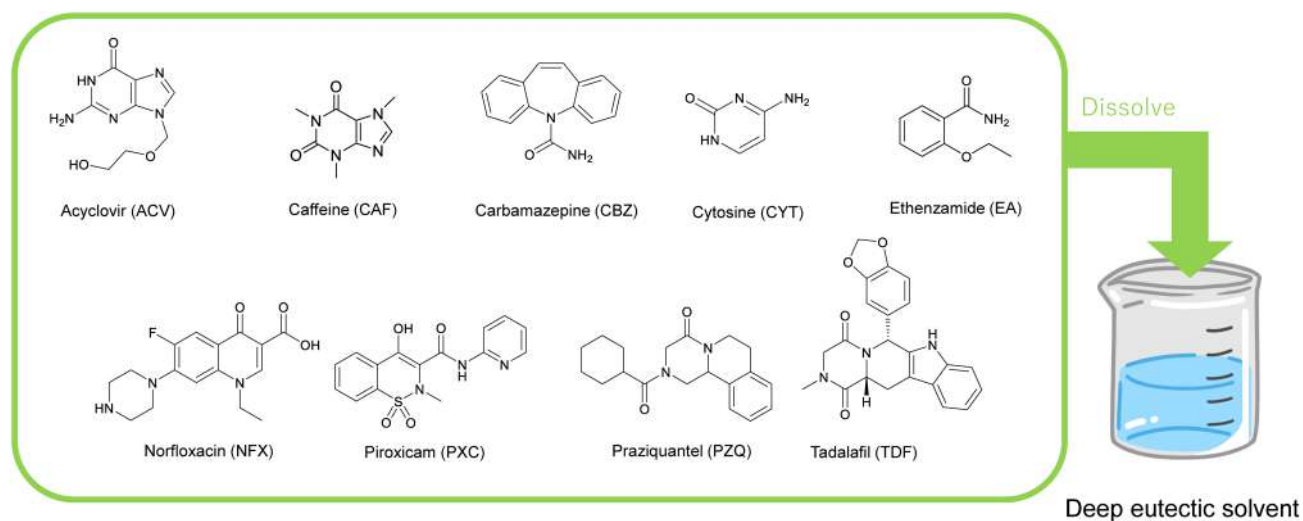


Fig. 3. List of Compounds Dissolved in DESs

In the study,¹⁷⁾ the API and the conformer for forming the multicomponent crystal (MA) were supplied from the DES mother liquor. The design of the DES mother liquor was crucial for crystallization. Three choline-based DESs (ChTs/MA, ChBr/MA, and ChCl/MA) were used. Nine APIs, which were the same as in previous studies (ACV, CBZ, CYT, EA, INA, NFX, PXC, PZQ, and TDF), were dissolved in the three DESs, yielding 27 solutions. In the dissolution step, the components were added to the DES at 100 °C and dissolved until almost no residue remained. Residual API was removed by vacuum filtration to obtain a saturated solution. The solutions were stored at 25 °C, and the precipitated crystals were recovered by filtration.

The crystals were identified by powder X-ray diffraction (PXRD) or single-crystal X-ray diffraction (SCXRD). For

CBZ, CYT, EA, NFX, and PZQ, cocrystals, salts, or salt cocrystals formed with MA. The EA–MA cocrystal and the NFX–MA–Ts monohydrate salt cocrystal were reported for the first time in the study. Precipitation did not occur under conditions where the model compound was barely soluble in the DES or the solubility hardly decreased after cooling to 25 °C.

The EA precipitate was a different crystal than the previously reported EA–MA 2:1 cocrystal (CCDC code: TIWPUN). SCXRD showed that this crystal was a new cocrystal with an EA:MA ratio of 2:1 (CCDC code: CIMVED). The TIWPUN crystal contained a large tubular void occupying approximately 20% of the cell volume, which indicated that solvent molecules are incorporated into the void during crystallization from an organic solvent. In contrast, the CIMVED crystal

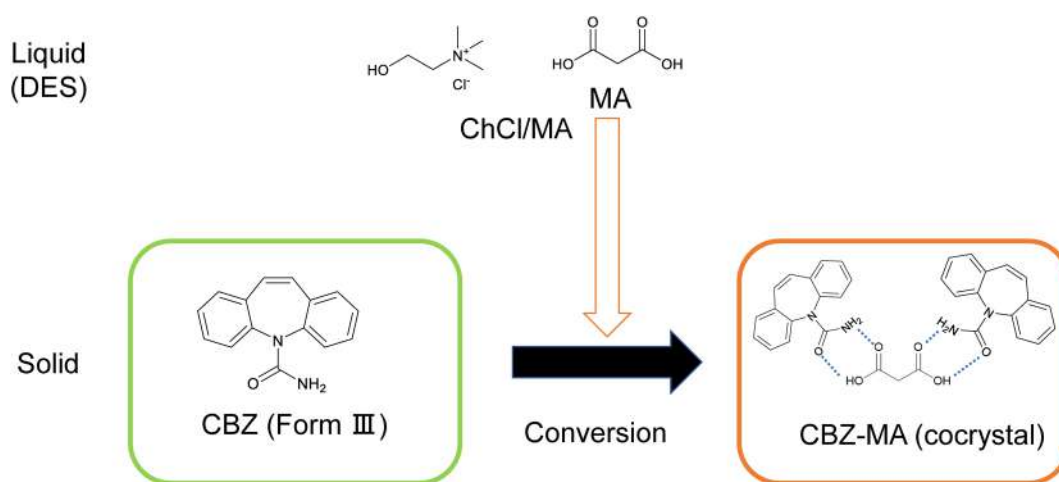


Fig. 4. Schematic of CBZ Conversion to CBZ-MA

Table 2. Bead Mill Conditions for CBZ and MA

No.	1	2	3	4	5	6	7	8
CBZ (g)	3.17	6.37	3.17	4.75	6.37	4.75	6.37	7.92
MA/ChCl (mL)	55	55	55	55	55	42	42	42
Ethanol (mL)	0	0	0	0	0	13	13	13
Beads (g)	0	0	148	148	148	148	148	148
Result	CBZ	CBZ	-	CBZ-MA +CBZ	CBZ-MA	-	CBZ-MA	CBZ-MA

exhibited fewer voids, suggesting greater stability than the TIWPUN crystal. The CIMVED cocrystal was obtained only with DES as the crystallization solvent, indicating that new cocrystals may be discovered by using the coformer as a DES component and omitting organic solvents.

5. Conversion of API to Cocrystals Using DES

The author conducted a practical study to obtain multicomponent cocrystals of a model API using a DES and a bench-top wet bead mill (Apex LABO, Hiroshima Metal & Machinery Co., Ltd., Hiroshima, Japan).¹⁸⁾ The model API was a CBZ Form III crystal, which forms cocrystals with MA,¹⁹⁾ and the DES consisted of MA and ChCl (ChCl/MA). The objective was to convert CBZ into a CBZ-MA cocrystal by suspending CBZ in the DES to form a slurry and processing the slurry in the bead mill (Fig. 4).

The bead mill used zirconia beads with a diameter of 0.3 mm; the operation time was 10 min; the temperature in the bead mill was maintained at 40 °C by circulating cooling water; and the peripheral mill rotation speed was 2.0 m/s. Eight conditions (Nos. 1–8) were investigated, in which the amounts of CBZ and DES, the presence or absence of beads, and the addition of ethanol were varied. Ethanol was added to reduce the DES viscosity (Table 2).

After wet bead milling, the precipitates were separated by centrifugation and evaluated by PXRD. Conditions Nos. 3 and 6 yielded no precipitate, attributed to an insufficient amount of CBZ relative to DES, causing all the CBZ to dissolve during wet milling. The precipitates from Nos. 1 and 2 showed XRD peak positions matching those of the CBZ Form III crystal, suggesting that these precipitates were pure CBZ. Because

no beads were added under these conditions, conversion to CBZ-MA likely did not occur. The PXRD pattern for No. 4 showed CBZ-MA and CBZ Form III crystal patterns, suggesting it was a mixture of CBZ-MA and CBZ. In contrast, the PXRD pattern for No. 5 closely resembled the CBZ-MA pattern, confirming that No. 5 was CBZ-MA. No. 5 contained a higher proportion of solid components in the system than No. 4 did, resulting in more frequent collisions between solids and higher conversion to CBZ-MA. For conditions Nos. 6–8, in which ethanol was added, the DES viscosity decreased, improving its flowability and facilitating handling during separation. For Nos. 7 and 8, only the PXRD pattern of CBZ-MA was obtained. Therefore, converting CBZ to CBZ-MA using DES was feasible.

These results can be used to scale up API preparation using DES. Furthermore, because MA acts as the precipitating solvent, excess MA is present compared with CBZ, and thus the solvent can be reused by replenishing only CBZ.

6. Conclusion

DES research and development is a new field; therefore, there has not yet been great progress in using DESs in pharmaceutical development. However, the recent surge in DES research may spark further research, particularly into the main advantages of DESs, including dissolving poorly soluble APIs and yielding new crystal forms. Although industrial applications of DESs face challenges regarding viscosity and separation, methods to overcome these challenges have been reported, including salting out or diluting with water. Selecting these methods according to the application may enable the preparation of DESs tailored for industrial use.

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The banner features a dark green background with a faint image of a modern building at night. On the left, the CPHI logo is displayed with the text 'by Informa' below it. In the center, the PMEC logo is shown with 'by Informa' below it. To the right, the text 'BDMAI@' is at the top, followed by 'Stall No.2127,' and 'API Zone, Hall 2' in large white letters. Below 'API Zone, Hall 2' is the word 'YASHOBHOOMI' in white. At the bottom left, 'INDIA' is written in white, followed by '23-25 NOV 2026' and 'IICC, Yashobhoomi, New Delhi' in green. In the center bottom, 'INDIA' is written in white, followed by '24-26 NOV 2026' and 'IEML, Greater Noida, Delhi NCR' in blue.

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The banner has a red background with a white box at the top left containing the GCS logo and the text 'GLOBAL ChemShow International Exhibition 2026'. To the right of this box, 'Hall no: 4' is written in white, followed by 'Bombay Exhibition Centre, Mumbai, India' in white. Below the white box, '14-15 December 2026' is written in white, followed by 'Booth Bookings now open - Secure your Premium Space today' in white. To the right of this text is an image of two glowing, crystalline structures. Below this, '300+ Exhibitors | 22,000+ Trade Visitors | International Attendees' is written in white. In the center, a white box contains the text 'Bulk, Fine & Speciality Chemicals, API's, Pharma Intermediates, Pharma Raw Materials, Pharma Excipients, Pharma Formulations, Custom Synthesis & Research, Contract Manufacturing, Process Technology Expo' in red. At the bottom, there are three logos: 'Media Partner GLOBAL INQUIRY MAGAZINE', 'Organised by NS Needs Information Services Ltd.', and 'Supporting Association BDMAI BULK DRUG MANUFACTURERS ASSOCIATION OF INDIA'. Below these logos, 'Contact : Ms. Roja Rani : +91-92461 83424 | www.globalchemshow.com' is written in white.

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