LITERATURE REVIEW

2.1 Introduction:

Chemotherapy-induced nausea and vomiting (CINV) is the term used to denote the side effects of cancer therapy. As the name suggests, it involves nausea and vomiting episodes in patients receiving chemotherapy. These episodes are sometimes so severe that it requires specialized treatment regimen which depend on the severity and type of chemotherapy patient is receiving. To decide the course of treatment, one need to understand the pathophysiology behind the CINV.

2.2 Pathophysiology of CINV:

CINV phases are divided into acute phase, delayed phase, or anticipatory phases, based on onset time:

a. Acute phase occurs within 24 hours after dosing of chemotherapeutic agent achieving maximal intensity within 5–6 hours [1-3].
b. Delayed phase often occurs after 24 hours of treatment and can continue till 5–7 days achieving maximal intensity by 48–72 hours [1,4].
c. Anticipatory phase is response that occurs before initiation of chemotherapy. It can be triggered by various factors such as smell, taste, sight, thoughts and anxiety [1, 5].

These different types of CINV suggests the presence of differences in pathological and physiological pathways [6, 7].

The CINV process involves a complex interplay between neurotransmitters and receptors at various anatomical regions. The nausea and vomiting centre at medulla oblongata, chemoreceptor trigger zone (CTZ) at brainstem, the vagus nerve and enterochromaffin cells in the gastrointestinal tract are located in the central and peripheral regions [8,9]. The central nervous system receives and process various stimuli related to emesis, send signals to different organs and play pivotal role in pathophysiology of CINV [10]. The threshold response varies from individual to induvial [11].

The three main neuro transmitters and receptors involved in the regulation of nausea and vomiting are serotonin (5-HT) associated with 5-hydroxytryptamine (5-HT3) receptor, substance P (SP) associated with neurokinin-1 (NK-1) receptor, and dopamine associated with dopamine (D2) receptor [12].

This advocates that the induction of emesis may be associated with different biological mediators through distinct pathways.

Clinical studies findings revealed that 5-HT/5-HT3 receptors play major role in the pathophysiology of acute CINV, but play lesser role for Delayed CINV [13-17].

Animal studies conducted suggests that synergistic effect may exist for 5-HT3 and NK-1 receptor antagonists in controlling acute CINV and Delayed CINV which improves the treatment efficiency in both types of CINV [18-22].

In addition, clinical trials conducted with 5-HT3 receptor antagonists and NK-1 receptor antagonist showed that both acute and delayed CINV follow different pathophysiological routes [23]. Multiple neurotransmitters such as dopamine acting on both central and peripheral nervous systems may also be contributing to both phases of CINV [24].

Additional research has also investigated that gamma-aminobutyric acid (GABA), histaminic and muscarinic receptors may also have role to play in management of nausea and vomiting [25].

The invention of new antiemetic drugs is often a challenging task. But the combination of existing antiemetic drugs in different dosage regimens can certainly be explored to aid effective treatment of both acute and delayed CINV.

Thus, detail understanding of the role of these transmitters and their CINV related mechanisms is required which certainly help in the development of novel effective antiemetic drugs and dosage regimens.

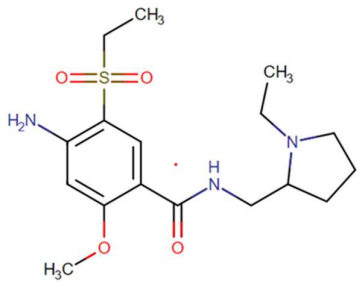
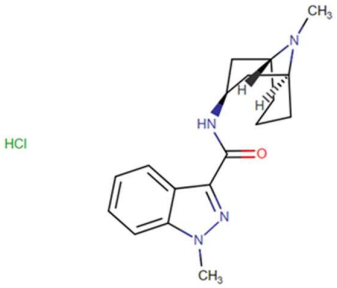
2.3 Current Treatments of CINV:

Table 2-1 Details of guidelines for CINV treatment [6]

Emesis risk	Recommendation
High	5-HT3 receptor antagonist + NK-1 receptor antagonist + dexamethasone or 5-HT3 receptor antagonist + Olanzapine + dexamethasone
Moderate	5-HT3 receptor antagonist (±NK-1 receptor antagonist + dexamethasone or 5-HT3 receptor antagonist + Olanzapine + dexamethasone or 5-HT3 receptor antagonist + dexamethasone
Low	Dexamethasone or Dopamine receptor antagonist OR 5-HT3 receptor antagonist
Minimal	No prophylactic antiemetic

2.4 Drug Profiles:

Table 2-2 Drug profiles [26-29]

Properties	Amisulpride	Granisetron HCl
Structure		
IUPAC name	4-amino-5-(ethanesulfonyl)-N-[(1-ethylpyrrolidin-2-yl)methyl]-2-methoxybenzamide	1-methyl-N-[(1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl]-1H-indazole-3-carboxamide hydrochloride
Molecular weight	369.479	348.88
Molecular formula	$C_{17}H_{27}N_3O_4S$	$C_{18}H_{25}ClN_4O$
Solubility in water (mg/ml)	0.293	>10
pKa (Base)	8.28	9
Log P	1.41	2.2
B/P ratio	0.98	0.86
Oral bioavailability	48%	60%
BCS class	II	III

Amisulpride:

Amisulpride is benzamide class atypical antipsychotic drug and a potent, selective dopamine D2 and D3 receptor antagonist [30]. Amisulpride follows linear pharmacokinetics, around 48% bioavailability, low protein binding (17%) and show elimination half-life of around 12 h [26,27]. It follows renal elimination in the form of parent compound [30]. The phenomenon of

blocking presynaptic D2/D3 receptors versus postsynaptic D2/D3 receptors is dose dependent [31].

For the past 30-40 years Amisulpride has been used orally in Europe for psychotic disorders [30]. From doses 50–1,200 mg/day, it has robust safety profile even in chronic usage [32]. The side effects of amisulpride in QT interval are minimal and with less extrapyramidal side effects [33]. In Feb 2020, FDA approved BARHEMSYS (an Intravenous 5 mg amisulpride) in prevention and treatment of postoperative nausea and vomiting (PONV) in single or in combination with other antiemetics [34]. 5 mg intravenous infusion injection is administered at the time of anaesthesia induction for prevention of PONV and 10 mg intravenous infusion injection is administered for treatment of PONV [34]. Two randomized, double-blind, placebo-controlled, multi-centre trials in patients established the efficacy of amisulpride in preventing PONV [34]. Clinical trial details of Amisulpride for the treatment of nausea and vomiting is presented in table 2-3.

Table 2-3 Clinical trial details of Amisulpride [52]

NCT Number	Study Brief	Study Status	Sponsor	Age	Phases	Enrolment	Completion Date
NCT05822713	Efficacy Comparison of Amisulpride with Placebo	Not started	Qilu Pharmaceutical (Hainan) Co., Ltd.	ADULT	PHASE3	516	2023-12
NCT01991860	US Phase III Study of APD421 in PONV	COMPLETED	Acacia Pharma Ltd	ADULT	PHASE3	364	2014-01
NCT01991821	European Phase III Study of APD421 in PONV	COMPLETED	Acacia Pharma Ltd	ADULT	PHASE3	368	2014-01
NCT02337062	Phase IIIb Study of APD421 in Combination as PONV Prophylaxis	COMPLETED	Acacia Pharma Ltd	ADULT	PHASE3	1147	2015-09
NCT05546359	Intravenous Amisulpride study in children	RECRUITING	Acacia Pharma Ltd	CHILD	PHASE2| PHASE3	410	2025-12
NCT02646566	Study of APD421 as PONV Treatment (Prior Prophylaxis)	COMPLETED	Acacia Pharma Ltd	ADULT	PHASE3	705	2017-01
NCT02449291	Study of APD421 as PONV Treatment (no Prior Prophylaxis)	COMPLETED	Acacia Pharma Ltd	ADULT	PHASE3	568	2016-07
NCT06585540	A Pilot Study to Evaluate Barhemsys for the Prevention of Postoperative Nausea and Vomiting in the Bariatric Surgery Population	RECRUITING	Benaroya Research Institute	ADULT	PHASE3	100	2026-01
NCT01857232	Dose-finding Study of APD403 to Prevent Nausea and Vomiting After Chemotherapy	COMPLETED	Acacia Pharma Ltd	ADULT	PHASE2	342	2015-02

Granisetron Hydrochloride:

Granisetron hydrochloride is an indazole class antiemetic drug and 5- HT3 receptor antagonist [29]. Granisetron is base with moderate lipophilicity and protein binding (65%) [35] and is available in intravenous injection, oral solution and tablets, transdermal system, and as extended-release injection [28].

The pKa was observed to be around 8.4, and it showed selectivity of binding greater than 1000:1 at 5-HT3 over other receptors [37].

Significant intersubject variability in PK parameters was observed regardless of dose, formulation or population [28]. After intravenous administration in healthy subjects, granisetron exhibits multiphasic plasma concentration profile [28].

The rapid initial decline of plasma concentration is due to extensive tissue uptake which can be observed from high apparent volume of distribution around 3 L/Kg. Granisetron shows mainly nonrenal clearance of around 0.6 L/kg/h. Around 12-13% of the drug is excreted as such through renal route. Granisetron has terminal phase half-life of 5.2 h [38]. Volume of distribution is high (around 4- 5 L/kg) in elderly patients of more than 65 years of age with around 40-45% lower total plasma clearance. Granisetron clearance is decreased in adult chemotherapy patients leading to longer half-life of around 11 h [39,40]. Pharmacokinetic studies conducted in paediatric cancer patients showed great variability and age-related dependence on pharmacokinetic parameters [41, 42].

The effect of antiemetic drug occurs on the basis of receptor occupancy at around 80 % at therapeutically effective doses in the case of 5-HT3 antagonists [43, 44].

After oral administration, granisetron is absorbed completely but due to first pass metabolism only 60% drug is bioavailable [28]. To enhance patient compliance and reduce fluctuations in plasma levels, a prolonged delivery transdermal system of granisetron (Granisetron Transdermal System) with tradename SANCUSO has been developed [45,46]. The patch is 52 cm^2 in area containing 34.3 mg of granisetron which delivers 3.1 mg of drug per 24 h for up to 7 days with peak concentrations reaching in around 2 days [45,46].

An extended-release formulation of Granisetron under trade name SUSTOL has been developed [28]. The formulation contains 10 mg of granisetron in form of once a weekly sustained release subcutaneous injection [47]. Peak plasma concentrations achieved within 12 hours in healthy subjects [48]. In patients, peak plasma granisetron concentrations were delayed compared to healthy subjects [47,48].

CYP3A5 enzyme variability leads to variable clearance of granisetron across the studies [49]. CYP1A1 enzyme is also responsible to the metabolism of the drug [50]. In patients with severe renal impairment, dose adjustment is not required due to low renal elimination of drug [51].

Clinical trial details of Granisetron for the treatment of nausea and vomiting is presented in table 2-4.

Table 2-4 Clinical trial details of Granisetron [53]

NCT Number	Study Brief	Sponsor	Age	Phases	Enrolment	Completion Date
NCT05434663	Safety Study of SUSTOL	Heron Therapeutics	ADULT	PHASE4	300	2025-10
NCT04912271	Transdermal Patch of Granisetron	Fudan University	ADULT	PHASE3	140	2023-12
NCT01662687	Efficacy and Safety study of SANCUSO	LG Life Sciences	ADULT	PHASE4	276	2012-11
NCT04472143	Transdermal Patch of Granisetron	Fudan University	ADULT	PHASE2	60	2022-12
NCT00273468	Transdermal Patch of Granisetron	Kyowa Kirin Co., Ltd.	CHILD, ADULT	PHASE3	630	2006-10
NCT02106494	ER Injection of Granisetron	Heron Therapeutics	ADULT	PHASE3	942	2015-05
NCT01596426	Transdermal Patch of Granisetron	Kyowa Kirin Pharmaceutical Development Ltd	CHILD	PHASE1	NA	NA
NCT01596413	Transdermal Patch of Granisetron	Kyowa Kirin Pharmaceutical Development Ltd	CHILD	PHASE1	NA	NA
NCT01659775	Transdermal Patch of Granisetron	LG Life Sciences	ADULT	PHASE4	389	2012-11
NCT05325190	Transdermal Patch of Granisetron	Tianjin Medical University Cancer Institute and Hospital	ADULT	PHASE2	57	2023-06
NCT01596400	Transdermal Patch of Granisetron	Kyowa Kirin Pharmaceutical Development Ltd	CHILD	PHASE1	19	2016-12
NCT00787566	Efficacy, Tolerability, and Safety studies of Intranasal Granisetron	Shin Nippon Biomedical Laboratories, Ltd.	ADULT	PHASE2	68	2009-05
NCT04085393	ER Injection of Granisetron	University of Alabama at Birmingham	ADULT	PHASE2	NA	2022-12

NCT Number	Study Brief	Sponsor	Age	Phases	Enrolment	Completion Date
NCT02457195	Transdermal Patch of Granisetron	Milton S. Hershey Medical Center	ADULT	PHASE2	50	2018-02
NCT04570592	Comparative study	Universiti Sains Malaysia	ADULT	PHASE2	126	2021-06
NCT06043336	Comparative study	Universiti Kebangsaan Malaysia Medical Centre	ADULT	PHASE4	134	2019-05
NCT03503292	Comparative study	Mayo Clinic	ADULT	PHASE4	92	2019-12
NCT00231478	Tonsillectomy or Adenotonsillectomy patient study	Hoffmann-La Roche	CHILD	PHASE4	171	2007-12
NCT06540885	Study in scoliotic Patients Undergoing Spine Surgery	University of Malaya	ADULT	PHASE4	74	2026-09
NCT03434340	Study in Intrathecal Morphine Induced emesis	Universiti Kebangsaan Malaysia Medical Centre	ADULT	NA	155	2019-04
NCT04918862	Comparative study	Cairo University	ADULT	PHASE3	210	2021-05
NCT05632224	Study in Laparoscopic Abdominal Surgery	Baskent University	ADULT	PHASE4	60	2023-01
NCT04899817	Study in Laparoscopic Cholecystectomy	Assiut University	ADULT	PHASE4	60	2022-04
NCT01352130	Study for comparative Effects on ECG, QTc	Tata Memorial Hospital	ADULT	PHASE4	70	2007-04
NCT04613726	Study on Cesarean Section surgery patients	Ataturk University	ADULT	PHASE3	120	2020-01

2.5 Sustained Release Injectable Formulations:

2.5.1 Introduction:

Sustained release injectable formulations are used to deliver drug over a period of several days, weeks, months or even years. Compared to conventional formulations, these long-acting formulations have several merits such as providing effect for long duration, reduced toxicity, dosage and frequency of administration.

There are several ways by which this prolonged drug release is achieved such as slow and controlled release, delaying the clearance from the body, modifying the resistance to enzymes, increased stability and extended half-life by modification of surfaces [54,55].

Various types of sustained release injectable formulations are described in figure 2-1.

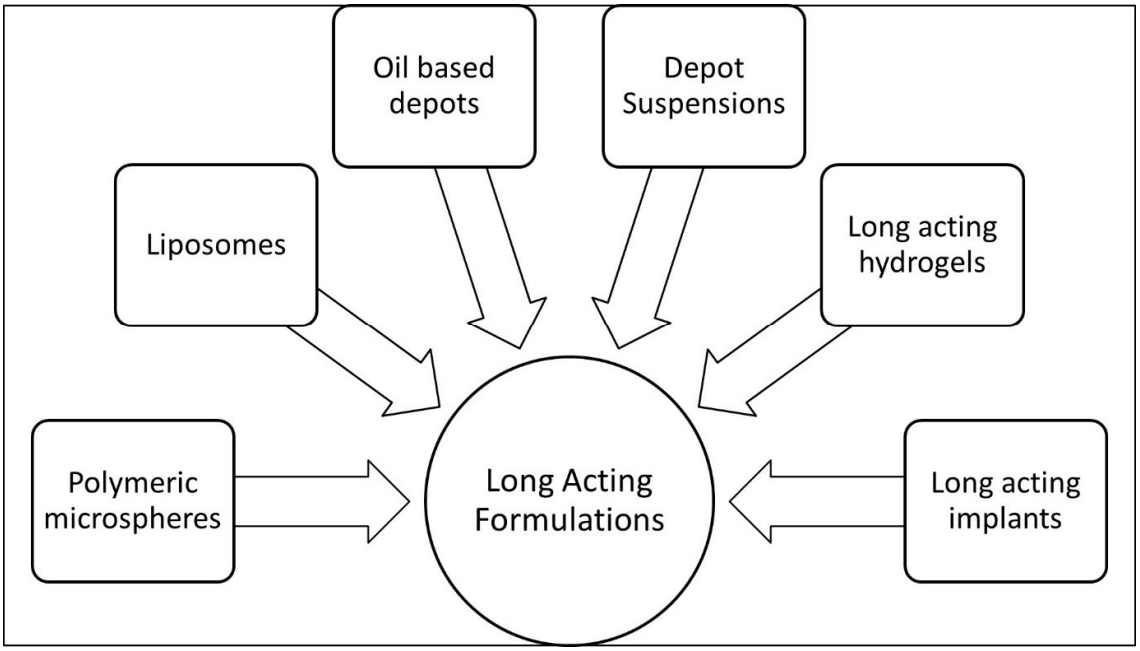


Figure 2-1 Types of Sustained Release Injectable Formulations

As discussed above, one of the strategies to alter the drug release to provide sustained action from delivery systems is micro-encapsulation [55]. Microcapsules are the drug delivery systems where solid or liquid active cores are surrounded by a polymeric shell, whereas when actives are dispersed or dissolved in polymeric materials, the delivery system is popularly known as microspheres [56,57].

The polymers which are used in microsphere formulation constitute natural polymers (*e.g.,* Chitosan, alginate, gelatin etc.), semisynthetic polymers [*e.g.*, Ethyl cellulose (EC), methyl cellulose (MC), cellulose acetate phthalate (CAP) etc.] and synthetic materials [*e.g.*, Polylactic

acid (PLA), Poly(lactic-co-glycolic) acid (PLGA) etc.]. Among these polymers, PLGA is biodegradable polymer which is the most popularly used and widely accepted by regulatory agencies to prepare polymeric systems [56]. Tailoring of release can be achieved by the polymer molecular weight, glycolic acid to lactic acid ratio, drug to polymer ratio and microspheres size and shape [58,59].

The primary mechanism of drug release from these depot systems comprises diffusion, dissolution followed by polymer erosion and degradation. The mechanism is described by initial burst release; release from porous structures formed; diffusion across the intact polymer surface; diffusion after entry of water into the polymer matrix; followed by erosion and degradation of polymer resulting in step wise drug release in sustained manner [60, 61,62].

The approved list of polymeric microspheres is presented in table 2-5.

Table 2-5 List of approved polymeric microsphere based LAF's [63]

API	Innovator brand	Innovator	Dosage form	Disease	Date of approval	First Generic available
Risperidone	RISPERDAL CONSTA™	JANSSEN	Microsphere intramuscular Injection	Schizophrenia and bipolar disorder	Oct 2003	N
Leuprolide acetate	LEUPRON DEPOT™	ABBVIE ENDOCRINE INC		Advanced prostatic cancer	Jan 1989	N
Naltrexone	VIVITROL™	ALKERMES		Alcohol dependence	Apr 2006	N
Octreotide acetate	SANDOSTATIN LAR™	NOVARTIS		Acromegaly	Nov 1998	N
Triptorelin pamoate	TRELSTAR ™	VERITY		Advanced prostatic cancer	June 2000	N
Minocycline hydrochloride	ARESTIN™	ORAPHARMA	Microsphere injection in periodontal sac	Adult periodontitis	Feb 2001	N

2.5.2 Janus Particles:

Janus particles are called after two-faced Roman god Janus because they exhibit distinct properties on different sides [64,65]. These particles consist of at least two distinct materials or compartments, each with unique properties (e.g., chemical composition, surface charge, or functionality) [64, 65]. The combination of these distinct properties within a single particle allows for versatile applications. Janus particles have been used for dual drug delivery. By incorporating two different drugs into separate compartments, they enable synergistic effects and reduce side effects [64]. Janus particles can carry therapeutic agents (e.g., drugs) and imaging or sensing modalities (e.g., contrast agents). This spatially controlled incorporation

allows for combined therapies not achievable with isotropic systems [65]. Due to their asymmetric structure, Janus particles can target specific cells or tissues more effectively. For instance, one side may be functionalized for cellular targeting while the other side carries therapeutic cargo.

In summary, Janus particles offer exciting opportunities for drug delivery, imaging, and personalized medicine. Their unique design allows for tailored approaches to address complex biomedical challenges.

Principle of formation of Janus particles:

Janus particle phenomenon involve phase separation where no drug was involved, has been attributed to the spreading coefficient theory governed by interfacial tensions [66]. Hemispheric nature of janus particles was attributed to equal interfacial tensions between the two polymers with the aqueous phase.

In a study conducted by Yan Liang Fan et.al, FDA-approved biocompatible polymers such as poly(lactic-co-glycolic) (PLGA) and polycaprolactone (PCL) were used to manufacture Janus particles (JP) using four model drugs. Instead of incorporating the drug using a blank Janus particle formulation, Janus particle were synthesized along with the drug using the emulsion solvent evaporation method. It was found that both the ratio of polymers and the net charge on the API were critical in formation of non-janus and janus structures. It was believed that drug molecule interacts with a polymer to change characteristics of the polymer in terms of water affinity. These scientific principles thus can serve as a scientific basis for the formation of nanometer to micrometer scale, drug-loaded Janus particles in a highly efficient manner [67].

The literature review of different microsphere and Janus particle formulations prepared using mainly PLGA and PCL polymers, dual-drug loaded and using emulsion-solvent evaporation techniques is given in table 2-6

Table 2-6 Literature review of microsphere's-based Drug delivery systems:

Formulation type	Drugs	Polymers	Therapeutic area	Highlights	Reference Number
Janus microspheres	Glibenclamide, Tolbutamine, Rapamycin and Lidocaine	PLGA and PCL	NA	Formulation feasibility	67
Janus microspheres	Curcumin, Quercetin, Acetaminophen and Naproxen	PLGA and PCL	Inflammation	Sustained release for dual drug loaded drug delivery system.	68
Janus microspheres	NA	PLGA, PCL and Precirol ATO 5 (Glyceryl palmitostearate)	NA	Formulation feasibility	69
Microspheres	Paclitaxel	PLGA and PCL	Cancer	Sustained release for drug for one month	70
Microspheres	Paclitaxel-EphA2	PLGA and PCL	Cancer	Sustained release for dual drug loaded drug delivery system.	71
Microspheres	NA	PLA and PCL	NA	Formulation feasibility	72
Microspheres	Palonosetron	PLGA	CINV	Sustained release drug delivery till one week	73
Microspheres in hydrogel	Palonosetron	PLGA and Poloxamer	CINV	Sustained release drug delivery till 60 days.	74
Microspheres	Erythromycin	PLGA and PCL	Infection	Stability and controlled release	75
Microspheres	Dextran	PLGA	NA	Formulation feasibility	76
Microspheres	Granisetron	Chitosan	Emesis	Mucoadhesive drug delivery through nasal route	77
Microspheres	Docetaxel and curcumin	PLA-PEO-PPO-PEO-PLA	Cancer	Sustained release providing high efficacy.	78

Formulation type	Drugs	Polymers	Therapeutic area	Highlights	Reference Number
Microspheres	Rutin Benzamide	PLGA	Cancer	Active targeting multidrug-resistance (MDR) associated phenotype	79
Double-layered microspheres	Cell homing factors (SDF-1) and osteoinductive growth factors (BMP-2)	Chitosan and alginic acid	Bone regeneration	Enhances the recruitment of osteogenic cells and osteoinduction,	80
Microsphere system	Naringenin and doxofylline	Chitosan-tripolyphosphate	Asthma	Improving efficacy	81
Microsphere	Prodigiosin Paclitaxel	PLGA-PEG	Cancer	Improving efficacy	82
Microsphere	Doxycycline	PLGA and PCL	Periodontal infections	Sustained release, enhanced efficacy up to 11 days	83
Microsphere	Clodronate	PLA and PCL	Osteoporosis	Sustained release up to one month	84
Microspheres in hydrogel	18β-glycyrrhetinic acid and bovine serum albumin	Poly (D, L-lactic) (PDLLA) in calcium alginate	Inflammation	Improved efficacy	85
Microspheres	Doxorubicin and paclitaxel	PLGA	Cancer	Improved efficacy	86
Microspheres	Transforming growth factor-β3 (TGF-β3) and dexamethasone with heparin	PLGA	Cartilage/ Bone disorders	Improved efficacy	87
Microspheres	Vancomycin HCl and dexamethasone	PLGA and PVP	Tissue engineering	Improved efficacy	88
Microspheres	Doxorubicin	Methacrylated alginate	Cancer	Improving potential chemotherapeutic delivery	89

2.6 Manufacturing methods of Janus particles:

2.6.1 Emulsion-Solvent Evaporation method

The emulsion-solvent evaporation method usually involves the formation of a single phase or double phase emulsion.

Single Emulsion Solvent Evaporation method

O/W method is method of choice for molecules having low aqueous solubility. This method involves solubilization of the water insoluble drug and polymers in an organic solvent; emulsification of organic phase in a dispersed phase; removal of the solvent from the dispersed phase by solvent evaporation using the continuous phase thus translating into solid followed by drying [90]. This O/W method is less suitable for water soluble drugs as they diffuse into the continuous phase during emulsification process, leading to drug loss [91]. Generally, solvents are eliminated from the system by evaporating them under vacuum or by extraction into the continuous phase. For solvent evaporation, the excess continuous phase is employed to enhance partitioning and evaporation.

Double Emulsion Solvent Evaporation method

The W/O/W double emulsion method include the formation of primary and secondary emulsions and is mainly suitable for encapsulating hydrophilic molecules. Primary emulsion is formed by dissolving hydrophilic molecule in an aqueous phase followed by adding this primary emulsion to the polymeric organic solution. Water-immiscible organic solvents such as methylene chloride, chloroform, ethyl acetate are most commonly used solvents. The primary emulsion is prepared either by vortex, homogenization or ultrasonication [92]. Commonly used emulsifier such as polyvinyl alcohol (PVA) can be used to prevent aggregation of droplets in the emulsion system.

The secondary emulsion is formed by adding the primary emulsion to aqueous phase containing PVA under continuous stirring or homogenization. Double emulsion formed is then transferred to an excess aqueous phase with or without surfactant to remove the organic solvent and harden the Janus particles. Then, the excess stabilizer solution or free drug is removed from the formed Janus particles by washing the Janus particles several times with water and then either lyophilized or vacuum dried [93]. As double emulsion is transferred into a large volume of aqueous phase, the organic solvent is diffused out [94]. This method is capable of generating Janus particles with relatively high drug entrapment, less losses and is suitable for thermolabile drugs [95].

However, hydrophilic drugs can leak from the polymeric phase to the outer aqueous phase which can hamper the encapsulation efficiency [96]. The solvent removal step is critical in the double emulsion method, as incomplete removal of solvent can lead to leaching of drug [97]. Schugenes et al. [98] studied the effect of molecular weight of polymers on emulsion stability prepared by the double emulsion technique by studying morphology and porosity of the microspheres prepared from L-polylactide polymer. The high molecular weight of polymers resulted in increased viscosity of the polymer solution which led to less stable primary emulsion and highly porous microspheres. The characteristics of microspheres can be custom-made by altering polymer type, stabilizer, the oil phase type, API to excipient ratio, and the process parameters [99].

2.6.2 Other methods

Coacervation

This method can be started by altering temperature, strength of ions, or other solvent addition. These changes results in the water removal from the phase [100,101]. The major steps in this technique includes the phase separation, adsorption of the coacervate around the drug molecules, and solidification [101,102]. Briefly, the phase separation process consists of formation of water in oil emulsion, formation of coacervate by slowly adding coacervating agent to encourage the phase separation, transfer of the mixture into heptane like medium for solvent removal and hardening of the Janus particles. This is followed by washing and drying under suitable conditions [103, 104].

Microfluidics

The preparation of Janus particles by microfluidics has been reported by several researchers. In microfluidics, a high-voltage electric field is applied to a polymer solution or melt, which is then ejected through a spinneret to form fine fibers. For Janus particles, a specially designed parallel spinneret is often used to simultaneously spin two different polymer solutions side-by-side. This results in fibers with distinct compositions on each side [105]. The advantages of using electrospinning for Janus particles include; high controllability which allows precise control over the thickness and pore size of the fibers, material versatility which enables the creation of fibers with various functionalities, structural flexibility that can aid in fibers with unique properties [106]. Briefly, microfluidic process is described as: preparation of two immiscible fluids, each containing different materials or functional groups, injection of fluids into a microfluidic device with precise control over their flow rates, formation of droplets with

distinct compartments and solidification of the droplets by polymerization or solvent evaporation, resulting in Janus particles with two distinct sides [107].

Masking

The phase interface method consists of trapping homogeneous particles at the interface of two immiscible phases. There are three types of phase interface methods such as liquid-liquid interface, liquid-solid interface and gas-liquid interface [108, 109].

Self-assembly

Self-assembly involves block copolymerization and competitive adsorption techniques [110]. The method results in producing block copolymers with well-defined geometries and compositions across large substrate varieties [111]. The production of different shapes of Janus particles is feasible by altering the molecular weights and cross-linking degree [112]. Use of two moieties which separate out from phase owing to different physiochemical properties is part of adsorption [110,113].

2.7 *In-vitro* drug release testing methods:

The drug release testing methods for Janus particles are similar to those which have been used for polymeric microspheres. Most common methods among these are dialysis, reverse dialysis, sample and separate method and flow through cell method [114].

In Dialysis Method, Janus particles are placed in a dialysis bag, which is then immersed in a release medium. The drug diffuses out of the particles through the dialysis membrane, and the concentration in the medium is measured over time [114]. The development of the *in-vitro* drug release by dialysis method involves selection of suitable dialysis membrane with an appropriate molecular weight cut-off (MWCO), appropriate hydrodynamics and an adequate release medium based on the physicochemical properties of the drug [115, 116].

In “sample and separate” technique, Janus particles are introduced into a tube or vials (for small volumes) and flask or bottle (for large volumes), and drug is analyzed from supernatant solution [117]. The drug release is affected by container type, agitation method, technique of sample separation and volume of sample to be tested [120]. The drug release from the Janus particles is measured by separating the supernatant from the Janus particles by centrifugation and precipitation [118]. For stable drugs, drug is analyzed from supernatant and for unstable drug, analysis is done from residue [119].

In the “flow-through cell” technique, drug release media is continuously circulated through a column containing drug-loaded Janus particles and drug content is measured in the eluent [119]. This method use continuously flowing solvent over the immobilized Janus

microparticles [118]. The flow-through cell mimics the bio relevancy due to lower volumes which is present in injection sites [118].

All three methods suffer from merits and demerits of their own and the selection of appropriate method depends on the feasibility and nature of the molecule and delivery system itself. However, specifically for Janus particles, sample and separate method is widely used in the literature due to its simplicity and little experimental set-up.

Apart from these three methods, conventional methods using United State Pharmacopoeia (USP) apparatus I (Basket) and II (Paddle) have also been explored [120,121]

Two examples of each *In-vitro* release testing (IVRT) method are presented in below table 2-7

Table 2-7 Examples of IVRT testing methods

Sr. No.	Highlights	Reference
1	Dialysis method using Slid-a-lyzer mini dialysis set-up for Acetaminophen and naproxen loaded janus particles prepared from PLGA and PCL.	68
2	Dialysis method using membrane with specified molecular weight for drug release determination of sample microspheres.	114
3	Sample and Separate Method for determination of drug release from palonosetron microspheres.	73
4	Sample and Separate Method for determination of drug release from palonosetron hydrogel microspheres.	74
5	USP Apparatus IV (flow through Cell) for determination of drug release from peptide microspheres.	120
6	USP Apparatus IV (flow through Cell) for determination of drug release from dexamethasone microsphere.	122
7	USP apparatus I (Basket) for determination of drug release from floating microspheres of lafutidine.	120
8	USP apparatus II (Paddle) for determination of drug release from floating microspheres of Metformin HCl.	121

2.8 Accelerated vs Real time drug release method

The sustained drug release from polymeric microparticles have been attributed to delayed degradation of the matrix which result in complex *in-vitro* drug release profiles [118]. The drug release studies of these formulations in long term conditions during product development is very lengthy and tedious process and can delay the development of LAF's. Thus modification of these methods to fasten the product development process is important [118]. Since last few decades, different research groups have developed modified IVRT methods to accelerate the drug release process by changing drug release medium temperature, composition, apparatus type and adding different surfactants [119].

Accurate prediction and discriminatory ability of these accelerated methods also aids in faster development process [122]. Accelerated methods also need to correlate with real time profiles in terms of mimicking all stages of erosion, diffusion and polymer degradation. These methods can be opted as quality control methods due to suitability at plant scale [123]. The increase in temperature is often selected based on the transition temperature of polymer suitable for all the drug diffusion phenomenon in accelerated manner [124]. Often, such studies are not designed at higher temperatures than transition temperature of polymers as the characteristics of polymer and product would get adversely impacted leading to change in release pattern [125]. The accelerated drug release method (at 55˚C) provided good correlation with the real time drug release (at 37˚C) for a peptide based long-acting injection. The method was also found to be discriminatory for the formulation and process changes [126].

Studies by Zolnik et al., showed that, the correlation between accelerated and real time drug release profiles was better for lower molecular weight PLGA than higher molecular weight PLGA polymers when tested in USP apparatus IV at different temperatures [122].

2.9 Design of experiments:

Design of experiments provide systematic approach of conducting experimental trials along with simultaneous analysis and interpretation of results [127]. When the trials are conducted systematically the bias and reproducibility issues get automatically resolved. Experimental designs generally include two major types: screening and optimisation designs.

The details of different types of designs commonly used in the formulation development and brief highlights of the same are outlined here. [128]

A] Screening Designs [129]:

The primary objective of a screening design is to select and identify the factors that can affect product performance. This is usually done by using fishbone diagram to list down all the factors involved in the development.

Three screening designs are most commonly:

1. 2-level screening designs: Screening linear terms
2. Plackett-Burman designs: Screening linear terms
3. Definitive screening designs: Used to understand square terms and 2-way interactions.

B] Response surface designs [130]:

Response surface design involve experimental combinations that can be used to optimize your product. Response surface methodology (RSM) is generally used to refine the developed model after screening designs to check whether the model contains any curvature.

The RSM involve the interaction terms that allows user to analyze the response curvature [130], which helps to

- Track how changes in different variables impact the selected response
- Selecting a variable level to optimize the response
- Choosing the operating ranges

Following designs are available:

1. Central Composite designs [130]

Central Composite designs are capable to fit full quadratic model. They are mostly used when further experimentation can be planned by including information from screening designs.

2. Box-Behnken designs

These designs usually are less complex due to lower number of runs with same number of factors as that of central composite deigns as they have less design points. Although they can estimate the first- and second-order coefficients; they are not able to include information from a screening design. These designs contain 3 levels for each factor, where central composite designs can have up to 5 levels for each factor. Box-Behnken designs does not include runs for factors at extreme settings.

C] Mixture designs [131]:

Mixture designs are a different class of response surface experiments where the investigation product consists of different types of components or ingredients. In such scenarios, the response is actually a function of the proportions of the different components in the mixture.

Commonly used mixture designs are

1. Simplex centroid
2. Simplex lattice
3. Extreme vertices

D] Taguchi design [132]:

A Taguchi design can allow user to select process that is more consistent in the operating conditions. It relies on the fact that not all factors can be controlled that cause variability. These factors are termed noise factors. This design help to identify control factors that can reduce the impact of the noise factors. During experimental trials, one can alter noise factors for forced variability and then optimize the control factors to make product or process robust. Any product or process designed using this approach tend to be more robust compared to other methods.

2.10 In-silico modelling:

2.10.1 Allometry:

As discussed in introduction section, Allometric scaling uses similarity of anatomy, physiology, and physiological parameters and is the most predominantly used method to calculate the plasma profile in human from animal data [133]. Allometric calculations involve use of volume of distribution (Vss) and clearance (CL) calculated for humans using preclinical species data. Various methods used to calculate Vss and CL are shown in table 2-8 and 2-9

Table 2-8 Methods Used to Predict Human Plasma Volume of Distribution (Vdss) [133-135]

Sr. No.	Method	Description of method	Equation
A)	Empirical		
1.	Simple allometry (SA)	Proportionality with body weight	$Vss = a\ (BW^b)$
2.	SA with f_{up}	Correction for Plasma protein binding	$\frac{Vss}{fup} = a\ (BW^b)$
3.	SA with f_{ut}	Correction for tissue protein binding	$\frac{Vss}{fut} = a\ (BW^b)$
4.	SA with f_{ut}/ f_{up}	Correction for both plasma and tissue protein binding	$\frac{Vss}{fut}/(fup) = a\ (BW^b)$
5.	SA: Average V_{ss} from preclinical species	Averaging principle for prediction	$Vss\ (human) = 1.99\ Vss\ average\ preclinical\ species^{0.413}$
6.	SA: Average V_{ss} from preclinical species with F_{ut}	Averaging principle for prediction	$\frac{Vt}{fut}(human) = 1.57\frac{Vt}{fut} average\ preclinical\ species^{0.84}$
7.	Single species: Rat	Proportionality for unbound drug	$\log\left(\frac{Vss}{fup}\right) human = [\log\left(\frac{Vss}{fup}\right) rat - 0.2247]/0.9271$
8.	Single species: Monkey	Proportionality for bound drug	$Vss\ (human) = Vss\ (monkey)$
9.	Single species: Monkey with f_{up}	Proportionality for unbound drug	$Vss\ /fup = Vss\ (monkey)/fup$
10.	Single species scaling: rat	Proportionality with rat	$Vss\ /fup = Vss\ (rat)/fup$
11.	Single species scaling: dog	Proportionality with dog	$Vss\ /fup = Vss\ (dog)/fup$
12.	Rat and dog	Proportionality	$\log Vss\ (human) = (0.07714 logVss\ (rat) X\ logVss\ (dog) + 0.5147 logVss\ (dog) + 0.586$

Sr. No.	Method	Description of method	Equation
B)	Semi mechanistic		
13.	Øie–Tozer method	Physiological parameter	$Vss(human) = Vp +$ (fup x Ve) + [(1 − Fup) x RE/I x Vp + Vr x fup/fut (human)
14.	Øie–Tozer method with QSAR	Use of Drug lipophilicity and ionization, plasma protein binding data.	$fut\ (calculated) = fut(human)$
15.	Arundel's model	Relationship between V_{ss} and distribution time constant of drug	$Vss = Vp +$ (Vt x Kput x fup)
16.	Arundel's model: Rat		Arundel constants for rat
17.	Arundel's model: Dog		Arundel constants for dog
18.	Jansson's model	Correlation between the partition coefficient values for different rat tissues.	$Vss = Vp + \sum(Vt\ x\ Kpt)$

Sr. No.	Method	Description of method	Equation
C)	Mechanistic		
19.	Tissue composition-based model 1	Partition coefficients are described from physiological data and compound-specific data. Drug ionization is considered partly while tissue binding is considered in overall.	$Vss = Vp + \sum(Vt\ x\ Kpt)$
20.	Tissue composition-based model 2	Method 19 except that tissue binding considered only in the water fraction	$Vss = Vp + \sum(Vt\ x\ Kpt)$
21.	Tissue composition-based model with unbound fraction	Similar to method 19, except that Drug ionization is fully considered. Drug ionization is fully considered.	$Kpu\ (calculated) = Kpu\ (human)$
22.	Tissue composition-based model with unbound fraction in muscle	Muscle unbound fraction considered	$Kpmuscle\ (calculated) = Kpmuscle\ (human)$
23.	Gastroplus method 1	Custom made software	NA
24.	Gastroplus method 2 with fraction unbound	Custom made software	NA

Table 2-9 Methods Used to Predict Human Plasma Clearance (CL) [136-138]

Sr. No.	Method	Description of method	Data required	Equation
A)	Empirical method			
a)	Allometry			
1.	Simple allometry (SA)	Proportionality to body weight	Data required in at least two species	$CL = a(BW)^b$
2.	SA scaling of unbound CL	SA with plasma protein binding correction	Data required in at least two species	$CL/Fu_p = a(BW)^b$
3.	Multiexponential allometry (MA)	Proportionality to body weight	Data required in at least two species	$CL = a(BW)^b + \frac{[1-(\frac{3}{2})b]}{[1-(\frac{1}{2})b]}\ X\ a(BW)^{0.9}$
4.	MA scaling of unbound CL	MA with plasma protein binding correction	Data required in at least two species	$CL/Fu_p = a(BW)^b + \frac{[1-(\frac{3}{2})b]}{[1-(\frac{1}{2})b]}\ X\ a(BW)^{0.9}$
5.	Two term power equation	Involves two exponential terms and MLP- maximum life span, BrW -brain weight	Data required in at least three species	$CL = a\ X\ BW^{\alpha} X\ (BrW)^{\beta}$ $CL = \frac{a\ X\ BW^{\alpha}}{MLP}$ MLP (years) = 185.4 X BrW0.636 X BW − 0.225
b)	Rule of exponent (ROE)			
6.	Rule of exponent	Requires correction factors based on exponent b, MLP- maximum life span, BrW -brain weight	Data required in at least two species	$if\ b \leq 0.55;\ CL\ Underpredicted$ $If\ b > 0.55\ and\ < 0.71;\ SA\ of\ CL$ $If\ b \geq 0.71\ and\ < 1: SA\ of\ CL \times MLP$ $If\ b \geq 1\ and\ < 1.3;\ SA\ of\ CL \times BrW$ $If \geq 1.3;\ CL\ overpredicted$
7.	Rule of exponent with fup	ROE with plasma protein binding correction	Data required in at least two species	CL/fup use.

Sr. No.	Method	Description of method	Data required	Equation
A) Empirical method				
c)	fu Intercept Correction Method (FCIM)			
8.	Vertical allometry: clogP>2)	Intercept method	Data required in at least two species	$CL = 33.35ml/min\ X\ (\frac{\alpha}{Rfu_p})^{0.77}$
d)	Liver blood-flow rate (LBF)			
9.	Liver blood-flow method	Correlation between animal and human	Human and animal liver blood flow, animal CL	$\mathrm{CL\ (human)\ =\ CL\ (animal)\ \times\ (human/animal)\ Qliver}$
10.	Liver blood-flow method with fup	Correlation between animal and human with plasma protein binding	Human and animal liver blood flow, animal CL, fup	$\frac{\mathrm{CL}}{\mathrm{fup}}\mathrm{(human)} = \frac{\mathrm{CL}}{\mathrm{fup}}\mathrm{(animal)} \times\ \mathrm{(human/animal)\ Qliver}$
e)	Single species method			
11.	Rat	For bound drug	CL in at least one species of rat, dog, or monkey.	$\mathrm{CL/kg\ (human)\ =\ CL/kg\ (rat)\ \times\ 0.152}$
12.	Dog	For bound drug		$\mathrm{CL/kg\ (human)\ =\ CL/kg\ (dog)\ \times\ 0.410}$
13.	Monkey	For bound drug		$\mathrm{CL/kg\ (human)\ =\ CL/kg\ (monkey)\ \times\ 0.407}$
14.	Rat Fup	Single species allometric scaling	CL in at least one species of rat, dog and fup	$\mathrm{CL\ (human)\ /fup\ =\ CL\ (rat)/fup\ \times\ (70/0.25)0.75}$
15.	Dog Fup			$\mathrm{CL\ (human)\ /fup\ =\ CL\ (dog)/fup\ \times\ (70/10)0.75}$
f)	Two species methods			
16.	Rat-dog -human	For bound drug	CL in species of rat, dog and monkey	$\mathrm{CL\ (human)\ =\ a(rat-dog)\ X\ (BWhuman)0.628}$
17.	Rat-monkey-human	For bound drug		$\mathrm{CL\ (human)\ =\ a(rat-monkey)\ X\ (BWhuman)0.650}$
B)	*In Vitro–In Vivo* Extrapolation (IVIVE) Methods			
a)	Use of physiological scaling factors			
18.	Using human microsomes/ hepatocytes	Well stirred model Parallel tube model Dispersion model	Drug disappearance rate determination	$\mathrm{CLint\ in\ vivo\ =\ CLint\ in\ vitro\ \times\ PBSF}$ $CLinvivo = (Qliver\ x\ RBP\ x \frac{CLintinvivo}{CLinitvivo} + Qliver\ x\ RBP$

Sr. No.	Method	Description of method	Data required	Equation
B)	*In Vitro–In Vivo* Extrapolation (IVIVE) Methods			
19.	Using a drug-specific scaling factor	Drug specific factors used	Drug disappearance rate determination	$\text{CLint in vivo} = \text{CLint in vitro} \times \text{PBSF x} \frac{CL_{int\ in\ vivo\ animal}}{CL_{int\ in\ vitro\ animal}}$ $\text{CLint in vivo animal} = \frac{CL_{H\ animal}}{\frac{f_{up}}{R_B}\left(1-\frac{CL_{H\ animal}}{Q_H}\right)}$ $\text{CLH rat} = \frac{CL_{total\ animal}}{R_{B\ animal}} - CL_{R\ animal}$
20.	Using an empirical scaling factor	Empirical scaling factors used	Drug disappearance rate determination	$\text{CLH} = \frac{Q_H\ X\ CL_{int\ in\ vitro\ human}\ X\ SF}{Q_H + CL_{int\ in\ vitro\ human}\ X\ SF}$
21.	Correction of protein binding in plasma	Fraction unbound used	Drug disappearance rate determination	$\text{CLH} = \frac{Q_H\ X\ f_{up}\ X\ CL_{int\ in\ vivo}}{Q_H\ + f_{up}\ X\ CL_{int\ in\ vivo}}$ $\text{CLH} = \frac{Q_H\ X\ f_{up}\ X \frac{CL_{int\ in\ vivo}}{f_{u\ micro}}}{Q_H + f_{up}\ X \frac{CL_{int\ in\ vivo}}{f_{u\ micro}}}$

Sr. No.	Method	Description of method	Data required	Equation
B)	*In Vitro–In Vivo* Extrapolation (IVIVE) Methods			
22.	Using recombinant P450 enzymes	Recombinant enzymes used	Intrinsic activity of enzymes	$\text{CLint} = \sum_{i=1}^{n} (CL_{int\ rec\ CYPi}\ X\ realtive\ abundance)\ X\ \frac{40\ mg\ microsome}{gliver}\ X\ \frac{25.7\ g\ liver\ weight}{kg\ body\ weight}$ $\text{CLint} = \sum_{i=1}^{n} (CL_{int\ rec\ CYPi}\ X\ RAF_i)\ X\ \frac{40\ mg\ microsome}{gliver}\ X\ \frac{25.7\ g\ liver\ weig}{kg\ body\ weigh}$ $\text{RAFi} = \frac{CL_{int\ HLM}}{CL_{int\ rec\ CYPi}}$
C)	Physiologically based approach for renal clearance prediction			
23.	For renal clearance	For calculating renal clearance	GFR, fu, p, CLsecr, and Pe	$\text{CLR} \approx [\ \text{GFR X Fup} + \frac{\text{CLsecr } X \text{ fub } X\ QR}{\text{CLsecr } X \text{ fu } X\ QR}\ x\ (1 - \text{freabs})$
D)	Computational approaches			
24.	Multiple linear regression method	Use of Statistics	Molecular weight, hydrogen bond acceptors	$\text{logCLH} = 0.433\ \text{X logCLrat} + \log \text{CLdog} - 0.00627\ \text{X MW} + 0.189\ \text{X Ha} - 0.00111\ \text{X logCLdog X MW} + 0.0000144\ \text{X MW2} - 0.0004\ \text{X MW X Ha} - 0.707$

2.10.2 Wajima-Dedrick plots:

In designing the clinical studies of drug molecules with complex biphasic profiles or the molecules for which minimum concentration data is required for ensuring safety and efficacy, the prediction of plasma profiles can be critical [139]. Several literatures reported prediction of plasma concentration profile for human using Dedrick and Wajima methods. The details of these methods are captured in introduction chapter. Few of the noted literature has been presented in table 2-10

Table 2-10 Literature review of Wajima-Dedrick plot method.

Sr. No.	Highlight	Reference
1	Base paper where Css-MRT method was successfully applied to four drugs.	140
2	The predictions for pharmacokinetic parameters within two-fold error were between 65-80% for eighteen compounds of Novartis.	141
3	Dedrick and C_{ss}-MRT approaches were used to determine pharmacokinetic parameters and human plasma profiles of 35 compounds of Johnson and Johnson.	142
4	Wajima superposition principle used to determine human plasma profiles using mean residence time. The predictions were accurate for 63% compounds within 2-fold error of Novartis.	143
5	Oral pharmacokinetic parameters were estimated using preclinical data of 4 compounds which was found to be within 2-fold error.	144
6	Fomepizole human pharmacokinetic parameters after intravenous/oral dosing were determined using allometric approach followed by normalizing curve method.	145
7	Evaluation of three methods for estimation of human pharmacokinetic of 10 drugs after intravenous administration in preclinical species.	146
8	Wajima approach was used to compare shape of plasma profiles in human from preclinical species. The results indicate that most of the results were found to be between low and medium.	147
9	Plasma profiles in humans were evaluated by integrating *in-vitro* intrinsic clearance (CL_{int}) into the Dedrick approach for 15 compounds using hybrid approach.	148
10	The prediction accuracy for oral pharmacokinetics was within 1.3-fold for nilotinib with oral bioavailability predicted was below 25%.	149
11	Prediction of half-life for 4 compounds in human using chimeric mice model showed that predicted half-lives were longer.	150

2.10.3 Dissolution, PBPK and PBBM modelling:

Several literatures reported dissolution, PBPK and PBBM models for prediction of pharmacokinetics. Few of the noted literature has been presented in table 2-11.

Table 2-11 In-silico model details from literature

Sr. No.	Highlight	Reference
1	Retrospective prediction of human pharmacokinetics of 26 compounds was performed using Gastroplus software with advanced compartmental absorption and transit model.	151
2	Development of sildenafil formulations for treatment of pulmonary hypertension using Gastroplus as part of in-silico modelling approach	152
3	Development of *in-vitro* dissolution model for describing the drug release from microspheres loaded with model drug Orntide. Degradation rate data of PLGA from literature was used to build the model and predict the release rate differences due to different lactic acid: glycolic acid ratios.	153
4	Prediction of pharmacokinetics and pharmacodynamics of modified release formulations using in-silico approach	154
5	Evaluation of time lag in the drug release for extended-release formulations using modelling approach for poorly soluble drugs.	155
6	Use of in-silico modelling approach to predict the *in-vivo* performance of anti-retroviral drugs with the help of *in-vitro* solubility and permeability studies.	156
7	Prediction of *in-vivo* pharmacokinetics of sildenafil CR tablet using in-silico modelling.	157
8	Calculation of ideal theoretical drug release curve using mathematical modelling that calculates dose and release constants.	158
9	Development of first order pharmacokinetic model for prediction of ADME of sustained release formulations using immediate and slowly releasing fractions.	159
10	Designing dosing strategies for long-acting dosage forms using different order mathematical equations.	160
11	Development of effervescent floating matrix tablet of diltiazem hydrochloride by calculating theoretical drug release profile.	161
12	Developing sustained release formulations by understanding on colonic reflux, gastric emptying phenomena for nine drugs from different biopharmaceutics classification systems using PBPK model.	162
13	Different mathematical models for estimation of drug-release were used to understand mass transport and drug release kinetics for nanosized formulations.	163
14	Development of PBPK model to design dosage regimens LAF's of antiretroviral drugs in paediatric patients	164
15	Use of PBPK modelling to simulate predictive long-acting formulations for anti-tubercular drugs.	165

Sr. No.	Highlight	Reference
16	To study the impact of formulation variables on ADME of self-microemulsions of simvastatin using PBPK modelling.	166
17	Justification of dissolution specifications for Dr. Reddy's formulation using PBPM coupled with IVIVR approach.	167
18	Use of Physiologically based pharmacokinetic modelling (PBPK) to study the impact of route of administration on *in-vivo* performance of tranexamic acid.	168
19	Use of Physiology-Based Biopharmaceutics Model (PBBM) was to support development of ribociclib immediate release formulations. The in vitro solubility and dissolution were correlated to absorption rate. It was found that absorption was permeability limited and hence slight changes in dissolution will not have significant impact on pharmacokinetics. PBPM offers building biowaivers, or justify the failures in dissolution similarity by building safe space.	169

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