INTRODUCTION

1.1 Chemotherapy-induced nausea and vomiting (CINV):

1.1.1 Background:

In 2022, over 20 million people were diagnosed with cancer and around 9.7 million deaths recorded worldwide as reported by American Cancer Society (ACS). The number of cancer patients is going to increase up to 35 million by 2050 [1].

Among the plethora of side effects caused by cancer and its treatment, chemotherapy-induced Nausea and vomiting (CINV) is most significant and troublesome side effect of cancer treatment [2]. CINV result in metabolism related disorders, dietary diminution and lack of appetite, worsening of the patient's morality and ultimately patient withdrawal from therapy [3].

Despite the development of new antiemetic agents, CINV remains bottleneck in the treatment for many patients. Moreover, identification of patients prone to CINV, adherence to treatment and handling different forms of CINV is challenging and need of time [4].

Multinational Association of Supportive Care in Cancer and the European Society for Medical Oncology (MASCC/ESMO), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have published dedicated guidelines for the treatment of CINV [5-7]. These guidelines classify the anticancer drugs treatment according to their 'level of emetogenicity', that is, the expected occurrence of nausea and vomiting [5,8]. These four levels are minimal (<10%), low (10–30%), moderate (30–90%), and high (>90%) [6].

The antiemetic guidelines recommend a predefined antiemetic treatment approach for each emetogenic level based on scientific knowledge. As most of the anticancer treatments are combinations of different antineoplastic agents, these predefined treatment approaches for CINV pose several limitations [9].

Learnings from the past clinical trials of antineoplastic agents conclude that the emetogenic potential is additive and hence nausea and vomiting caused by anticancer drugs varies as per the combination used in the treatment protocol [8].

The incidence and severity of CINV is affected by a number of factors, such as dosage and administration, route of administration, disease as well as inherent patient characteristics such as age, gender, physiology, prior exposure to chemotherapy, disease conditions, pregnancy, alcohol or drug exposure etc. [7, 10]. The role of these variations on the outcome of clinical

trials is not clear due to lack of evidences from clinical studies and hence the international antiemetic guidelines does not take these variations into account [6,7,11]. As a result, the classification of emesis risk from international guidelines cannot be considered perfect and need modifications as required [9].

1.1.2 Current Treatments:

Chemotherapy-induced nausea and vomiting (CINV) can hamper the quality of life of cancer patients [12]. It occurs in up to 80% of patients suffering from cancer and taking chemotherapy [13,14].

CINV occurs in two well distinguished phases; acute and delayed. Acute phase appears within 1–2 h of anticancer drugs administration and can stay up to 24 h while delayed phase occurs almost 24 h after anticancer drugs administration [15].

Current treatment of CINV involves use of multiple therapeutic agents due to high receptor heterogenicity. (See figure 1-1)

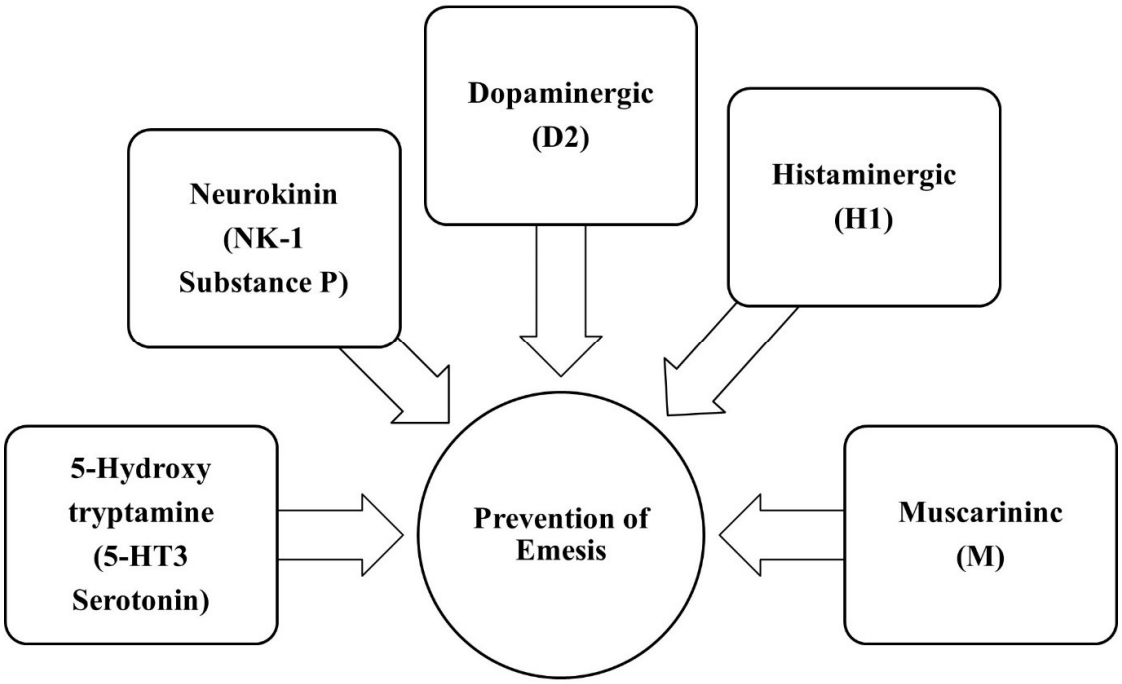

Figure 1-1 Receptors involved in Emesis [16]

The histaminergic and muscarinic receptors are mainly involved in regulating anti-nausea effect. The antihistamines are also used for treatment of motion sickness which mainly involves

effects due to M1 anticholinergic receptors and H1 antihistaminic receptors [17, 18]. Anticholinergic agents act by blocking the pathway to the brain stem from the inner ear and the vomiting centre [17, 19]. Olanzapine, which blocks dopaminergic, serotonergic, alpha-adrenergic, and histaminic receptors [20], has also been proved useful in controlling nausea [21].

Acute CINV is treated with serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists as first line of treatment [22]. For delayed CINV, however, there are limited treatment options available [23-25].

Current prophylaxis for delayed CINV include prescribing a NK-1 receptor antagonist (Aprepitant, Fosaprepitant, Casopitant, Rolapitant etc) along with a 5-HT3 receptor antagonists (Granisetron, Ondansetron, Dolasetron etc) and corticosteroids such as dexamethasone for prevention of CINV in patients receiving highly emetogenic chemotherapy (HEC), and a 5-HT3 receptor antagonist and dexamethasone in patients on moderately emetogenic chemotherapy (MEC) [22, 26].

However, differences in pharmacokinetics and pharmacodynamics amongst the available antiemetic agents can affect their efficacy in discrete clinical scenarios. Drugs or formulations with long duration of action and a good safety profile will play important role in such situations. This is important for effective prevention of CINV and manging the patients receiving multiple treatments or geriatric patients and/or patients who have with comorbidities and cognitive impairment [22].

1.1.3 Choice of drugs:

Clinical trials conducted on granisetron suggest the superiority of granisetron over other drugs from similar class in preventing delayed phase of emesis that appear after 24 h [27]. The effect is due to its ability to supress the activity of the vagus nerve connecting the vomiting centre in the medulla oblongata [2].

Dopamine (D2 and D3) receptors antagonist Amisulpride is approved from 1980s for psychosis treatment. It has a wide safety profile at doses of 400– 800 mg/day [28]. In a pilot investigational study, ondansetron and intravenous dose of amisulpride administered in combination resulted in preventing emesis in 83% of patients [29]. Amisulpride is also approved for prevention of PONV [30]. In a clinical trial, oral amisulpride at a dose of 10

mg daily was found to be safe and superior to placebo [31]. The complete response (CR) rate in the delayed phase was 46% with 10 mg amisulpride, compared to 20% with placebo [31].

A new long-acting formulation of granisetron (5-HT3 receptor antagonist), has been developed for treatment of both acute and delayed CINV under the brand name SUSTOL [2]. This formulation utilizes Biochronomer™ technology which is composed of viscous tri (ethylene glycol) poly (orthoester) polymer [32]. A single subcutaneous (SC) injection result in maintaining therapeutically significant concentration levels of granisetron over 5 days [2, 32]. However, this product is recommended to be administered in combination with other antiemetics and is only for moderately emetogenic chemotherapy.
Another formulation of granisetron in the form of transdermal patch under brand name SANCUSO has been approved. This product is recommended for the prevention of emesis in adults receiving MEC or HEC [33]. However, SANCUSO suffers from delayed Tmax effect and has not been effective in treating acute emesis phase [33].

United States Food and drug administration (USFDA) has approved Amisulpride intravenous injection (5mg/10mg) for treatment of post-operative nausea and vomiting in Feb 2020 which acts on dopaminergic receptor [34]. Amisulpride is available in Europe and other markets for treatment of psychosis and schizophrenia at high doses (50-1200 mg) [35,36]. Recently clinical trials also have been conducted for use of amisulpride in CINV [29]. However, there is no long-acting formulation available for Amisulpride.

Currently these two are the only long-acting formulations available in the market to treat both acute and delayed CINV. Hence there is a need and scope in design of sustained release formulations of antiemetic drugs which can deliver the drug for longer duration i.e., over a weeks' time.

1.2 Hypothesis:

Almost all patients receiving chemotherapy experience CINV even after optimization of antiemetic treatments [10]. Functional Living Index-Emesis (FLIE) is a matrix which assesses quality of life of cancer patients, states that CINV has intense adverse effects on quality of life of patients [37-39]. This is also associated with considerable financial burden associated with CINV due to the ever-increasing costs of antiemetic medications. Some of the examples include, intravenous palonosetron and Fosaprepitant costing $188.70 and $262.65 per dose respectively [40]. An earlier cohort study carried out in around 19139 patients calculated the mean expenses of CINV treatment visits to be around $5299 for the one-month chemotherapy cycle and average patient associated costs to be $731 [41]. It was observed that, for considerable number of patients, the cost of managing the treatment is more than the cost of chemotherapy itself [42].

To address the cost to benefit issue, optimization of CINV treatment is required. Although, extensive research has been done on the management of acute CINV, limited knowledge is available regarding various types of CINV. In a recent study of 240 patients receiving MET, higher incidence of delayed CINV was reported in comparison with acute nausea and vomiting [43]. This demonstrates the challenges in the treatment of delayed CINV which are difficult to reverse [16, 44]. Preventing the initial CINV is the best management as far as anticipatory CINV is concerned [45]. It is essential to identify and investigate the role of different available treatment options in these types of CINV. Although, multiple regulatory groups have published guidelines for emesis treatment, most of the patients do not adhere or do not receive guideline-recommended antiemetic therapy [46-48]. It was estimated that only 29–57% of patients that receive antiemetic therapy were found to be consistent with available guidelines [49,50]. Increased compliance to recommended regimens can lessen the CINV frequency [49,50]. Increasing the patient awareness by healthcare professionals by providing education regarding the antiemetics and their administration shall also enhance the treatment adherence [51].

As the commencement of emesis phases usually overlay after first day of treatment, it remains a challenge to decide suitable antiemetic dosage regimen. The MASCC and ASCO guidance's prefer granisetron/ondansetron plus dexamethasone for acute CINV and delayed CINV for patients on chemotherapy [52]. However, this regimen is not much effective in treatment of delayed phase [52]. Hence, optimization of treatment strategies for multiple-day chemotherapy is necessary as part of future research area.

Lastly, interindividual variations in the antiemetic drugs response is proving to be bottleneck in developing effective regimens [53]. Variability in individual genomes make it difficult to design and develop potential candidates for antiemetic therapy [53]. Recent progress has been made on decoding genetic variabilities [53,54]. Only limited information on receptor polymorphism is available in domain [54]. Future research into the genetic variability of CINV will aid in the development of personalized treatment options [53].

The treatment options which address both acute and delayed phases of emesis occurring during chemotherapy are thus very limited and less effective. The marketed formulations available are SUSTOL (Granisetron SC Injection) and SACUSO (Granisetron transdermal patch) for once a weekly treatment [32,33]. Currently no generic is available for both the drugs due to patent protection and proprietary polymer technology. However, these individual formulations still require combination with other antiemetics for effective treatment [33].

The available anti-emetic dosage regimen recommends combination of two or three antiemetic agents to control the delayed emesis in moderate and high emetogenic chemotherapy treatment [4].

There is need of formulations which provide effective treatment and patient compliance. This can be achieved by designing long-acting dosage forms with combination of two drugs, which provide sustained drug release up to one week [55].

Comparative *in-vivo* studies in human are required for approval of generic or branded product which are costly and time consuming [56]. Prediction of pharmacokinetics in human from *in-vitro* and *in-silico* studies is facilitated by regulatory agencies through modelling and simulation approach to reduce cost and create platform for future research [57].

Currently there is a need of *in-silico* pharmacokinetic models which can mechanistically link *in-vitro* and pharmacokinetic properties to predict *in-vivo* performance of antiemetic drugs.

1.3 Research Statement:

1.3.1 Benefits of combination of drugs for effective treatment:

Polypharmacology is “the design or use of pharmaceutical agents that act on multiple targets or disease pathways” as defined by the American National Library of Medicine (NLM) [58]. It is emerging science where treatment of complex and incurable diseases can be sought with use of multiple drug therapies [58, 59]. It combines basic concepts from systems biology to understand the reasons for disease emergence and finding the effective treatment options. In

general, polypharmacology address both drug combinations and drugs acting on multiple targets at the same time [60]. The problem of combining multiple drugs is that one needs to take care of their pharmacokinetic and pharmacodynamic properties while designing suitable dosage forms [61]. One of the strategies is to load two or more drugs acting on different receptors onto a single drug-delivery system to deliver drugs at the site of action.

Simultaneous drug delivery through multiple drug loading based on polymeric depot systems can be good strategy to achieve enhanced efficacy [62]. Using advanced drug delivery systems and use of physical pharmacy principles, dual-drug delivery form complex nano or microsystems is achievable [62].

To achieve maximum drug effect, drugs with different properties and mechanism of action should be used at their suitable dose and regimens in the treatment [63].

1.3.2 Long-acting Formulations (LAFs):

Long-acting formulations (LAFs) are used to deliver the drug over a period of several days, weeks, or even months [64]. Compared to fast releasing dosage forms, LAFs provide sustained drug release for longer period of time thereby reducing frequency of administration and toxicity [64]. The techniques to achieve long duration of release comprise of release rate alteration, changing the drug distribution/clearance and enzymatic resistance, etc. [65,66].

One of the ways to alter the drug release from delivery systems include drug entrapment or encapsulation in which APIs are dispersed or dissolved in polymeric materials to form microparticles or microcapsules [67, 68]. The polymers which are generally used in these drug delivery systems include natural (such as chitosan, gelatin etc.), semisynthetic [such as methyl cellulose (MC), ethyl cellulose (EC), cellulose acetate phthalate (CAP), etc.], synthetic materials [such as Poly (lactic- co-glycolic acid) (PLGA), polylactic acid (PLA), Polycaprolactone (PCL) etc.]. Amongst all polymers, PLGA is the most versatile biodegradable material to prepare depot polymeric systems, encompassing around 45% of overall markets. The drug release can be tailored by amending the molecular weight of PLGA, drug to polymer ratio, the ratio of glycolic acid to lactic acid and particle size [69,70]. 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 from the surface; release through the 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 [71, 72,73].

Janus particles are named after the two-faced Roman god Janus because they exhibit distinct properties on different sides [74]. These particles consist of two distinct materials or compartments with unique properties such as chemical composition, surface charge, or functionality [74-76]. 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 [77]. 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 [78]. Due to their asymmetric structure, Janus particles can target specific cells or tissues more effectively [78].

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.

1.4 In-silico modelling:

1.4.1 Introduction:

Cost- and time-effective formulation design can be achieved by adapting new tools such as Quality by Design and *in-silico* modelling & simulation [55]. Model informed drug development utilize quantitative models in product development to enhance and simplify decision making processes. First one is Physiologically-based pharmacokinetic modelling (PBPK) which interpret and predict absorption, distribution, metabolism and excretion (ADME) properties of API inside the body [79] and second is Physiologically-based biopharmaceutics modelling (PBBM) which forms link between *in-vitro* data and *in-vivo* performance [80]. In both the models, the data is used from preclinical and clinical studies to predict the *in-vivo* performance of formulation and understand the underlying physiological processes. Developing such models will help in robust product development and maximize *in-vivo* success.

In-silico models which can integrate the formulation and process attributes with physiological parameters to establish link between *in-vitro* drug release and *in-vivo* drug release using mechanistic understanding are essential to optimize the formulation and reduce the commercial

problems that usually arise in complex products [67,80]. In-silico biopharmaceutics models consider factors that can critically impact the product performance. They incorporate mechanistic elements such as particle size and/or drug release and establish their impact on ADME of drug and formulation [80]. After fixing these elements, PBBM modelling can be used to study the impact on critical material attributes (CMAs) and critical process parameters (CPPs) to establish a safe space via either *In-vitro in -vivo* correlation (IVIVC) or relationship (IVIVR) along with virtual Bioequivalence (VBE) simulations. This approach will facilitate the establishment of biorelevant tests from starting phase of development to product management and removing the costly *in-vivo* BE studies, leading to overall cost reduction [80].

1.4.2 Allometry:

In the drug discovery process significant workforce and investments are required to assess the *in-vivo* pharmacokinetic (PK) properties of potential drug candidates [81,82]. Systematic research is under progress for predicting the PK behaviour of drug candidates with minimal *in-vivo* testing's [83, 84]. During early drug development stages, the prediction of the pharmacokinetic (PK) profiles of new drug candidates in human is essential and important to determine the suitable dosage regimen in first-in-human (FIH) studies and to reduce the risk to volunteers [85]. Reliable prediction of human PK profiles by using different methods have been of significant interest [86-94]. Different techniques have been used to determine parameters such as steady state Vd (*V*dss), clearance (CL), or to estimate plasma profiles in human subjects [88,89,91,95,96]. These methods include allometric scaling, IVIVE, and PBPK modelling.

Allometric scaling uses sameness in anatomy, physiology, and physiological parameters and is the most predominantly used method to calculate the plasma profile in human from animal data [87]. In this method, the power function is used to scale the animal parameters to human [97-99]. It is an empirical method and to improve the prediction accuracy, many modifications have been applied on this method. Modifications such as corrections for brain weight (BrW), maximum life-span potential (MLP), the scaling of unbound CL, inclusion of *in-vitro* metabolic data or application of the "rule of exponents" (ROEs).

IVIVE to predict clearance using *in-vitro* microsome or hepatocyte assays is most popularly used method. Further extension of this method includes corrections for incubation matrix binding, plasma protein binding, or additional scaling factors [90,92]. Monte Carlo partial least square method, semi mechanistic Øie–Tozer (ØT) method and whole-body mechanistic PBPK model methods have been also explored to successfully predict *V*dss and CL [92, 100, 101].

1.4.3 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. The traditional Dedrick method is a simplest method reported in the literature which uses body weight as correlating factor [102,103]. Wajima et al. method also known as superimposition method (named the Css-MRT approach), adopts normalizing the time with MRT and the plasma concentration with *C*ss [103]. Dedrick and the Css-MRT methods showed comparable accuracy in predicting plasma profiles [104]. Css- MRT method is superior over Dedrick as it can incorporate predicted CL and *V*dss values from any method instead of relying on simple allometry [105].

1.4.4 PBPK and PBBM:

PBPK models which uses advanced compartmental absorption and transit (ACAT) models are superior to all existing pharmacokinetic models [106]. The prediction of plasma profiles after oral administration (p.o.) requires bioavailability and absorption rate values, which cannot be predicted through allometric methods as described previously. In some studies, the average F and ka observed from the animal species have been used in the prediction after extravascular administration [104,105]. This has led to biased estimation and thus PBPK models offer suitable alternative in prediction of bioavailability and absorption parameters [106]. Due to increasing popularity of these models, a regulatory PBPK expert consortium has been established [106,107].

Current treatment option and recommendations require the administration of more than one drugs being dosed at multiple times at fixed intervals [108]. These multiple dosing administrations resulted in fluctuations and variable results for safety and efficacy of the formulation resulting to poor quality-of-life with ultimately discontinuation of prescribed treatment [109]. To address this, LAF's of water soluble and insoluble drugs in polymeric or lipidic matrixes or depots have been developed which are of micron or nanometer size [110, 111]. Since few decades, the focus of scientist is on developing smart drug carrier systems to deliver the drug at intended site of action [112]. These approaches comprise of multiple drug combinations with different release rate kinetics. For developing generic versions of approved medicine, development of biorelevant and bio-discriminatory testing methods are required [113]. However, conventional PK modelling for such differentiated formulations is difficult and continuous improvement for these models is required followed by development of predictive IVIVC models with regulatory acceptance [114].

1.5 Aim:

The aim of this research was to design and develop once-weekly long-acting formulations and pharmacokinetic models using *in-vitro in-silico* tools.

1.6 Objectives:

The objectives of present work were:

- ✓ To develop *in-silico* pharmacokinetic model which will guide in the design and development of sustained release formulations and predict *in-vivo* performance.
- ✓ Development of formulations which will provide sustained drug release over a period of one week.
- ✓ To predict the *in-vivo* pharmacokinetics in humans using *in-vitro* data and the developed *in-silico* model.

1.7 Plan of work:

A) Design stage: Development of *in-silico* models

1. Development and verification of pharmacokinetic models
2. Identification of target plasma concentration using dissolution and PBPK model
3. Development of dissolution model for target dissolution profile
4. Identification of desired dose

B) Development Stage: Analytical method and formulation development

1. Pre-formulation
2. Analytical method development
3. Formulation development

C) Evaluation Stage: *In-vitro* and *in-silico* evaluation

1. *In-vitro* characterization studies
2. Prediction of *in-vivo* pharmacokinetics using the developed PBPK model
3. Virtual bioequivalence studies
4. Predictive IVIVC for establishment of design space

1.8 References

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