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Nasal route: an alternative approach for antiemetic drug delivery

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Introduction: Antiemetic drugs are used in the treatment of nausea and emesis. Development of novel delivery systems for antiemetic drugs, as an alternative to conventional preparations, is important in terms of good patient compliance and improving bioavailability. The nasal route offers unique superiorities, such as fast and high drug absorption, and high patient compliance. Therefore, a considerable amount of research has been carried out on the development of nasal delivery systems for antiemetic drugs.

Areas covered: This review deals with the importance of nasal delivery of antiemetic drugs and the studies performed on this subject. The first part of this review summarizes the properties of the nasal route, its advantages and limitations, parameters affecting drug absorption through nasal mucosa, nasal passage pathways and general approaches to improve nasal transport. The second part reviews the studies conducted on the development of nasal delivery systems.

Expert opinion: Due to its superiorities, the nasal route could be considered as an attractive alternative to oral and parenteral routes. To overcome the barrier properties of the nasal epithelium and to enhance transport of antiemetic drugs, several approaches, including permeation enhancers, *in situ* gel formulations and micro- and nanoparticulate systems, have been evaluated. The results obtained are promising and indicate that nasal formulations of some antiemetic drugs may enter the market in the near future.

Keywords: antiemetic drugs, dimenhydrinate, domperidone, granisetron, metoclopramide, nasal *in situ* gels, nasal microspheres, nasal route, nasal solutions, ondansetron, promethazine

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1. Introduction

Nausea and vomiting are the most common adverse effects observed among cancer patients receiving chemotherapy. Antiemetic drugs are used to prevent nausea and vomiting that may occur following cancer chemotherapy and radiotherapy. Furthermore, these drugs are used in cases of motion sickness as well as in treatment of postoperative emesis. Antiemetic drugs are frequently delivered by oral and parenteral routes in treatment. [1-4]. There are certain difficulties in oral or intravenous (i.v.) administration of antiemetic drugs for patients undergoing chemotherapy treatment. The most important limitation to oral delivery is to be discharged from the drug by emesis before systemic absorption. In addition, most of the antiemetic drugs administered by an oral route are exposed to hepatic first-pass effect, and consequently their bioavailability can be decreased or inter-subject variability may occur.

The parenteral route has also several disadvantages, such as poor patient compliance, high cost, safety consideration and non-feasibility of self-administration. Development of alternative drug carrier systems to be administered by non-invasive

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Article highlights.

- Antiemetic drugs are usually used as oral and parenteral preparations in the treatment. However, both oral and parenteral routes have some limitations. To overcome the disadvantages of current dosage forms of antiemetics and to improve the antiemetic treatment, development of alternative drug delivery systems would be useful.
- Nasal route is one of the most attractive alternatives due to its several advantages such as rapid and high drug absorption capability, overcoming the hepatic first-pass effect and good patient compliance. However, drugs are cleared from nasal mucosa without allowing sufficient time for absorption due to fast mucociliary clearance on nasal mucosa.
- A considerable amount of study has been performed on the development of nasal drug carriers of antiemetics. Mucoadhesive polymers have been used to provide more contact period between drugs and nasal mucosa in order to suppress mucociliary clearance. The effect of permeation enhancers to improve barrier properties of nasal membrane has also been evaluated.
- It is anticipated that nasal formulations of antiemetic can be on the market in the near future to improve the quality of life of patients who suffer from nausea and emesis particularly during and after cancer chemotherapy.

This box summarizes key points contained in the article.

routes (nasally, pulmonary, transdermally, etc.) aims to improve patient's compliance to treatment and to overcome other problems. With this approach, promising results have been reported on delivery of antiemetic drugs particularly by the nasal route.

Nasal delivery of drugs has been used for many years to achieve a systemic effect. Nasal drug delivery is suggested as one of the most convenient alternative administration route to parenteral injection. The main reason for this is the high permeability of the nasal epithelium due to its thin structure and wide blood vessel network. Therefore, the nasal route has several advantages such as rapid and high drug absorption capability, overcoming the hepatic first-pass effect on the drugs and good patient compliance [5-11].

In this article, general information about the nasal route has been reviewed and studies related to the development of nasal formulations of antiemetic drugs including metoclopramide (MTC), ondansetron (OND), granisetron (GRN), dimenhydrinate (DMH), domperidone (DOM), promethazine (PRM) used in antiemetic treatment have been summarized.

2. Nasal route

The nose is divided into two symmetrical nasal cavities with the septum in the middle. It has three regions with different epithelial structure, which are filtration (vestibule), respiratory and olfactory regions [10]. Drugs delivered nasally are absorbed in the respiratory part, which has a wide surface area (150 cm^2) than the other regions [9,12]. The nasal route has many advantages and some limitations compared with the other delivery routes (**Table 1**) [5,7,13].

The nasal mucus is 5 μm thick and consists of an outer viscous mucous layer (gel) and an aqueous (sol) layer on the mucosal surface [13]. The mucous secretion consists of 95% water, 2.5 – 3% mucin, 2% electrolytes, proteins, lipids, enzymes and antibodies [14,15]. The mucin is responsible for the gel-like appearance of the mucus. The epithelium is covered with a new mucous layer approximately every 10 min [13,16]. Substances inhaled from outside by respiration are held by the mucus in the nasal cavity or dissolved in the mucus and pushed to the nasopharynx to be discharged to the gastrointestinal tract. The clearance of mucus and absorbed/dissolved substances into the gastrointestinal tract is called 'mucociliary clearance' [16,17]. This mechanism is actuated through the combined undulating motion of the mucous layer above and the cilia below [13]. The cilia are the hair-like structures on the surfaces of epithelial cells. A ciliary cell contains approximately 300 cilia. Each cilia is 5 – 10 μm long and 0.1 – 0.3 μm wide [18,19].

3. Factors affecting drug absorption through nasal mucosa

The primary factors affecting nasal absorption of drugs depend on the physicochemical properties of drugs and the formulation parameters. Besides anatomical and physiological factors, pathological conditions and environmental conditions strongly affect drug absorption in the nasal region [5,7,8,12,13,20-30]. The effects of these parameters on nasal absorption are summarized below (**Table 2**).

4. Passage of drugs through nasal mucosa and enhancement of nasal transport

Drugs should first pass through the nasal mucous layer and then the epithelial layer to achieve systemic effect. The passage of drugs across nasal mucosa is achieved via three different pathways [19]. The first pathway is the *paracellular passage* that is related to the intercellular cavity and tight junctions. This route is particularly the main pathway for polar drugs [31-33]. The second route is the *transcellular passage* achieved by passive diffusion or an active transport mechanism [34]. This route is an important pathway in the absorption of lipophilic drugs or the molecules recognized by the membrane (transport via active carrier). The third pathway is the *transcytosis*. It is a specific pathway for particles, in which the particles are taken inside the vesicle, then enter the cell and, finally, are stored in the interstitial space [19,35-36].

When drugs are applied as simple solutions by nasal route, bioavailability of drugs would be low due to the short retention times of formulations in the nasal mucosa depending on mucociliary clearance [7]. Therefore, nasal absorption and

Table 1. Advantages and limitations of nasal route.

Advantages	Limitations
Fairly wide absorption area	Limited application volume (25 – 250 μl)
Highly vascularized epithelial layer and rapid blood flow	Low permeability for drugs of molecular weight higher than 1000 Da
Porous and thin endothelial basement membrane	Irritation potentials of some drugs on the mucosa
Rapid absorption and fast onset of therapeutic action	Enzymatic barrier for drugs (especially peptide and proteins)
Overcoming hepatic first-pass metabolism	Pathologic conditions
Low risk of overdose	
Alternative for drugs undergoing degradation in gastrointestinal tract	
Good patient compliance	

bioavailability can be enhanced by preparation of mucoadhesive gel or powder systems [5,7,20,37-41]. In the study performed by Ozsoy *et al.* [38], nasal gel formulations of ciprofloxacin were prepared with bioadhesive polymers (hydroxypropyl methylcellulose, hydroxyethylcellulose and methylcellulose). It was observed that the nasal gel prepared with hydroxypropyl methylcellulose performed similar bioavailability as with the oral route. It was also found that the nasal bioavailability of the drug can be significantly improved by adding 1% (w/w) Tween 80 as a permeation enhancer.

Drugs with low molecular weight (MW) can be absorbed through nasal mucosa at a rate that can almost be compared with i.v. delivery [8,42]. However, the nasal mucosa is an obstacle to passage of drugs that are larger than 1000 Da [22]. Recent studies have focused on the nasal delivery of drugs with high MW. Moreover, nasal preparations of certain drugs (salmon calcitonin, nafarelin acetate, cyanocobalamin, desmopressin acetate, etc.) are available commercially. A review article that comprehensively considers nasal delivery of drugs with high MW has been recently published [43].

Different approaches are used to enhance permeation of drugs through nasal mucosa. One of the most popular approaches is to include permeation enhancers in the formulation. The most frequently used permeation enhancers are chelating agents, surfactants, fatty acids and cyclodextrins (CDs) [12,20,44-48]. These agents enhance absorption of drugs through nasal mucosa by various mechanisms of action, which are inhibition of enzyme activity, lowering mucous viscosity, suppressing mucociliary clearance, opening tight junctions and improving solubility of drugs [7,23]. Enzyme inhibitors [12,20] and a prodrug approach [20] are also used to improve nasal absorption. In addition, chitosan has been extensively investigated as a nasal absorption enhancer [44].

In recent years, there have been attempts to enhance nasal passage with particulate systems providing sufficient residence time for drug absorption in the nasal cavity [12,20,46,49]. Particulate systems inhibit mucociliary clearance in the nasal cavity to enhance drug residence time in the mucosa and establish tight contact between nasal mucosa and the drug to ensure localization of high drug concentration. It also enhances nasal absorption by opening tight junctions between epithelial cells [8,20,49-50]. Particulate systems (nano- and microparticles) are matrix systems in which the drug is dispersed in polymeric material [51]. Retaining these systems in nasal mucosa depends on the strong mucoadhesive property of the polymer used. Mucoadhesion is a phenomenon of interaction forming between mucin and polymer [17]. The parameters affecting mucoadhesion are related to the polymer characteristics (MW, cross-link density, free chain length, etc.), environmental factors (hydration, swelling, pH, etc.), physiological factors (mucociliary clearance, ciliary beat frequency) and pathological factors [6,20,52-53].

5. Nasal delivery of antiemetic drugs

Antiemetic drugs are used in the treatment of nausea and emesis in various cases such as migraine, postoperation, motion sickness, pregnancy and so on and particularly during and after cancer chemotherapy or radiotherapy [4]. These drugs play an important role in the quality of life of patients. Since these drugs usually have a short half-life (3 – 6 h), some of antiemetic drugs may have to be used three or four times a day. Oral and parenteral preparations of antiemetic drugs are frequently used in treatment [54]. Drugs given orally are usually discharged by emesis before their systemic absorption. Thus, the oral efficiency of drugs is limited. Besides, most orally delivered drugs are exposed to hepatic first-pass mechanism, which affects bioavailability of the drug. As is well known, the parenteral route has important disadvantages such as poor patient compliance, high costs, safety considerations and the non-feasibility of self-administration. Therefore, alternative delivery routes are suggested for antiemetic drugs, and a considerable amount of study has focused on the subject [55]. The most attractive alternative is the nasal route due to its advantages. The most important limitation for nasal delivery is the fast mucociliary clearance. Drugs are cleared from nasal mucosa without allowing sufficient time for absorption due to clearance of drugs on nasal mucosa. Mucoadhesive polymers are used to provide more contact period between drugs and nasal mucosa in order to suppress mucociliary clearance.

When the studies on nasal delivery of antiemetic drugs are reviewed, it has been observed that certain different

Table 2. Parameters influencing nasal absorption of drugs.

	Physicochemical properties of drugs	Ref.
Chemical structure	Salt or ester forms of a drug molecule affect the nasal absorption	[15]
Polymorphism	Different polymorphs of drugs have impact on nasal transport due to the difference in solubility	[6,10]
Molecular weight	It is well known that nasal absorption rate of drugs with high molecular weight (> 1000 Da) has been significantly decreased	[17]
Molecular shape	It has been reported that molecular shape of drug molecules play a role in nasal delivery, and molecules in cyclic structure is absorbed easily than those of linear structure	[106]
Lipophilicity	Lipophilicity of drugs increases their nasal transport. Nasal absorption of hydrophilic and high-molecular weight drugs (such as peptide and proteins) is fairly low	[16,18-19]
pKa	According to pKa–pH partition theory, non-ionized drugs are well absorbed through nasal mucosa compare with ionized drugs	[15,16,18]
Particle size	Uptake of powder formulations on respiratory tract is dependant on density and shape of particles and their content of humidity. Particles in the size of 10 – 20 μm are deposited on nasal mucosa	[20,107]
	Formulation parameters	
pH and osmolarity	Formulation pH has an important role in nasal transport due to ionization of the drug. Besides, if it is possible, pH of formulation should be adjusted to physiological condition to avoid irritation	[15,16,18]
Viscosity	High viscosity of formulation leads to increase in residence time of drugs on mucosa and thus nasal transport of drugs	[15,16]
Concentration of drugs	Application of drug at low concentration is preferred to reduce its possible irritation risk on nasal mucosa	[103]
Formulation	Nasal drainage and precision of dosage applied is a potential problem. Localization of drugs on the nasal mucosa can be provided with the application of gel formulations. Usage of nasal emulsion and ointment formulations is limited	[7,16,22]
Device type	It has been reported that devices used to apply the formulation to nose affected drug absorption	[4,22]
	Other factors	
Anatomical factors	Nasal volume and length, surface area of epithelium, cell structure, angle between nostril and nasal cavity, deviation	[4]
Physiological conditions	Nasal blood flow, composition of nasal secretion, pH, mucociliary clearance, ciliary beat frequency, coordination and extent of ciliary movements, mucous volume, enzymatic activity	[6,18,21]
Pathological conditions	Rhinitis, asthma, sinusitis, nasal polyps, Kartegener's syndrome, Sjögrens syndrome, structural dysfunction etc	[4,22,106]
Environmental factors	Smoking, changes in temperature suddenly, humidity, etc	[1,23]

polymer-based pharmaceutical forms (solution, gel, powder and microspheres) have been developed and evaluated *in vitro/ex vivo/in vivo*. In these studies, Poloxamer 405, Pluronic 127, gellan gum, sodium carboxymethyl cellulose, Carbopol 981, chitosan and degradable starch have been used as polymer. In addition, the formulations included hydroxypropyl cellulose, polyvinyl alcohol, hydroxypropyl methylcellulose, sodium alginate, microcrystalline cellulose polymers to enhance mucoadhesiveness, and bile salts, protamine sulfate and poly-L-arginine and CDs as permeation enhancers. The antiemetic drugs that have been studied for nasal delivery in the literature include MTC, OND, GRN, DMH, DOM and PRM. The chemical formula, MW, solubility and log P, pKa and half-life ($t_{1/2}$) of these drugs are given in **Table 3** [56,54].

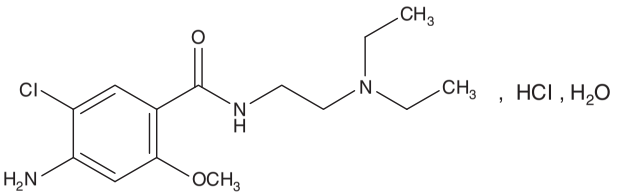
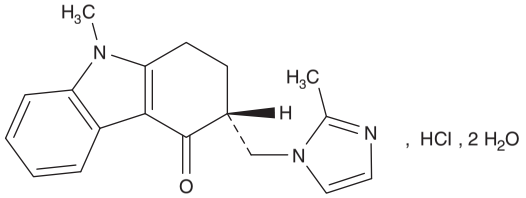
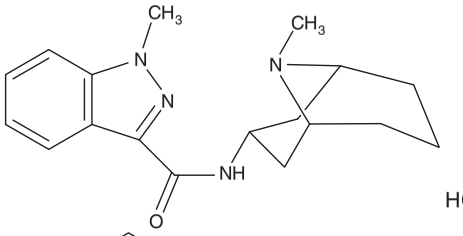
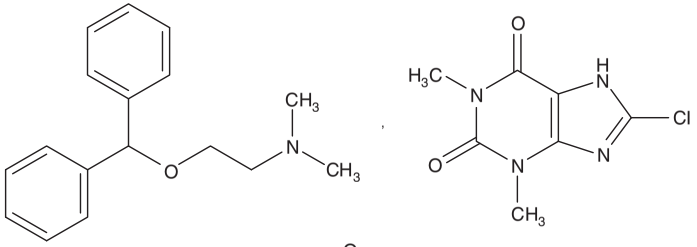
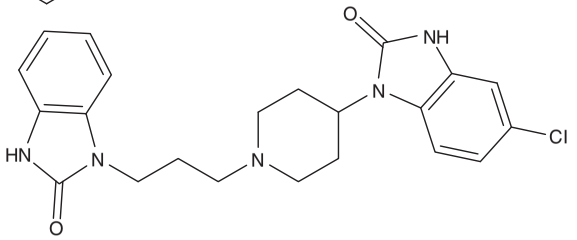
5.1 Metoclopramide

MTC HCl is a potent antiemetic that is used in the treatment of nausea and emesis arising due to various pathological reasons. MTC is well absorbed orally and achieves its peak plasma concentration (C_{max}) in 1 – 2 h [54]. However, it is exposed to hepatic first-pass effect, and its bioavailability varies between subjects from 32 to 100% [57]. Its oral tablet (10 mg) and solution (1 mg/ml) and i.v./i.m. (5 mg/ml) preparations are available commercially.

Alternative application routes of MTC have been investigated to overcome the disadvantages of both oral and i.v. delivery. Several studies have been published on the delivery of MTC by the transdermal route [58,59] and nasal route [60-73].

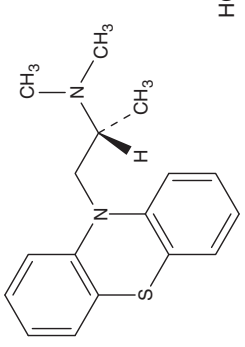
Considering the studies on the delivery of MTC by the nasal route, it has been seen that solutions, gels, lyophilized

Table 3. Physicochemical properties of antiemetic drugs.

Drugs	Chemical formula	MW	Solubility	Log P	pKa	$t_{1/2\ (h)}$
MTC		354.3	Very soluble in water	2.66	0.42 and 9.71, 9.36	5 – 6
OND		365.9	Sparingly soluble in water	2.4	7.7	5.7
GRN		348.9	> 10 mg/ml in water	2.6	9.4	4 – 6
DMH		470.0	Slightly soluble in water	-0.39	-	1 – 4
DOM		425.9	Practically insoluble in water	2.4	7.9	7

DMH: Dimenhydrinate; DOM: Domperidone; GRN: Granisetron; MTC: Metoclopramide; OND: Ondansetron; PRM: Promethazine.

Table 3. Physicochemical properties of antiemetic drugs (continued).

Drugs	Chemical formula	MW	Solubility	Log P	pKa	$t_{1/2}$ (h)
PRM	 HCl	320.9	Very soluble in water	4.4	9.1	12 – 15

DMH: Dimenhydrinate; DOM: Domperidone; GRN: Granisetron; MTC: Metoclopramide; OND: Ondansetron; PRM: Promethazine.

powder and microspheres enhancing residence time of the drug in the nasal mucosa have been investigated. The disadvantage of gels is their failure regarding accurate dosing due to their viscosity. The selection of delivery device is required for mucoadhesive powders. Preparation of microspheres is more difficult than the other formulations. Therefore, *in situ* gel-forming solutions, which are easy to prepare, are the most frequently studied nasal dosage form. *In situ* gels are in solution form at room temperature. However, the gel-forming process occurs depending on the gel-forming mechanism of the polymer immediately after nasal delivery. These mechanisms are *in situ* formation based on i) physiological stimuli (pH and thermally), ii) chemical reactions (ion-sensitive and enzymatic cross-linking, photo-polymerization) and iii) physical mechanism (diffusion and swelling) [74].

In situ gels of MTC were prepared with Poloxamer 405 [60]. Chitosan, hydroxypropyl cellulose, polyvinyl alcohol and carbopol polymers were added into nasal formulations to increase mucoadhesion of poloxamer gels. In addition, polyethylene glycols (PEGs, PEG 400 and PEG 6000) were also used to asses the effect of gels on $T_{sol-gel}$ temperature. The formulations containing Poloxamer 407, carbopol, PEG 400 and benzalkonium chloride were administered to New Zealand white rabbits and compared with i.v. and oral solution (**Figure 1**). The C_{max} of MTC from nasal solution was found to be higher than that of the oral formulation and its T_{max} value was relatively lower than that of oral solution. Relatively higher bioavailability was obtained from nasal gel (69.1%) when compared with oral solution (51.7%) due to overcoming the hepatic first-pass effect. The effect of poloxamer was attributed to the decrease in mucous viscosity and its flexibility, thus affecting the barrier property of the mucus to enhance transcellular passage [75,76]. Carbopol, an anionic polymer, is also known to improve the paracellular passage of drugs [77]. It can be emphasized that the *in situ* nasal gel allows precise dosing and could be an alternative to the oral route in terms of better patient compliance.

In a similar study, Pluronic 127 was used as polymer to prepare *in situ* gel of MTC [61]. Mucoadhesion of gels was improved with hydroxypropyl methylcellulose, sodium carboxymethyl cellulose and sodium alginate and drug release was modified with PEG 6000. An increase in gel viscosity led to a fall in $T_{sol-gel}$. Inclusion of PEG 6000 reduced the mucoadhesion strengths of all formula, while increasing gelation temperature by 3 – 4°C. It was stated that the *in situ* nasal gel of MTC has a potential use with ease of delivery, accuracy of dosing and prolonging the residence of the drug on nasal mucosa.

Gellan gum, an anionic polymer, which has an extremely effective gelation property in the presence of mono or divalent cations in nasal secretion, was used to prepare *in situ* gels of MTC [62]. Histological studies showed that the formulations caused no damage to nasal mucosa. I.v. and oral solution, and nasal gel were administered to rabbits at a dose of 10 mg. The application of nasal *in situ* gel improved the

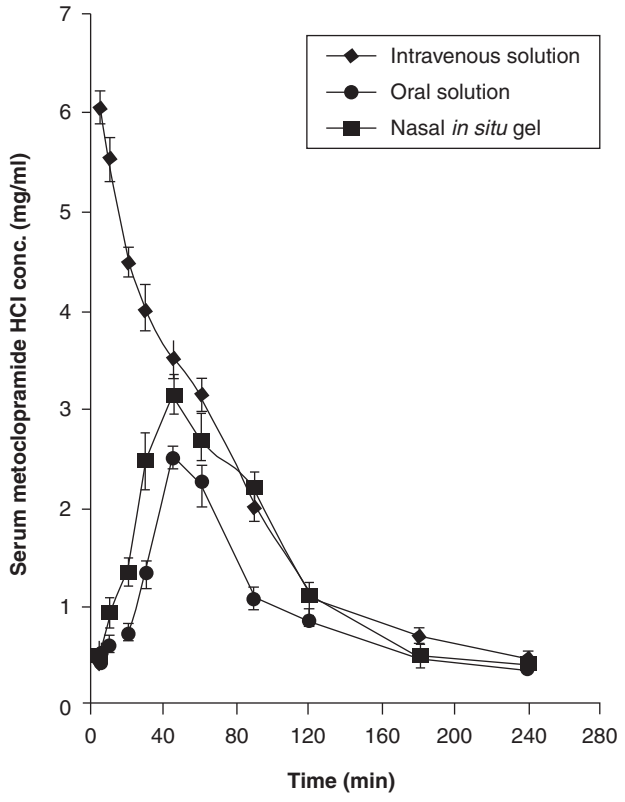


Figure 1. Mean serum concentration–time profiles following administration of i.v. and oral solutions or nasal *in situ* gel of metoclopramide MTC in rabbits.
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absolute bioavailability and shortened the T_{max} value when compared with oral solution.

In another study, *in situ* gel-forming solutions of MTC with sodium carboxymethyl cellulose were prepared for nasal application [63]. Polymeric solution administered by nasal route to rabbits (15 mg/kg) improved the absorption of MTC compare with aqueous solution of MTC. Higher bioavailability of polymeric solution than the aqueous solution was explained by an increase in residence time of the polymeric formulation on the mucosa.

Various permeation-enhancing agents are used to improve transport of drugs via the nasal route [12,20,45-48]. Sodium deoxycholate, sodium cholate, chitosan (high and low MW), protamine sulfate and poly-L-arginine were used to enhance nasal permeation of MTC [64]. MTC was well absorbed at 90% in the rat sample nasal cavity after almost 60 min. The highest increase in absorption was obtained with sodium deoxycholate. In the other study, the absolute bioavailability of nasal spray containing 0.5% sodium cholate and oral solution was calculated as 87.21 and 55.62%, respectively [65]. The authors indicated that the nasal spray solution of MTC can be used in urgent treatment of severe emesis as it ensures fast and high systemic drug absorption.

Nasal spray of MTC and its commercially available tablets were tried on healthy subjects in terms of tolerability [66]. Tolerability studies were evaluated based on the gastrointestinal symptoms (e.g., epigastralgia, pyrosis, nausea and vomiting) for at least 3 months. It was determined that nasal spray was tolerated by 100% and tablets by 78%, indicating that nasal spray can be an effective alternative to oral delivery.

Solution, powder and microspheres of MTC have been prepared for nasal delivery [67]. Microcrystalline cellulose and degradable starch were used in powder form and microspheres, respectively. Nasal absorption of MTC from these formulations was followed in healthy subjects. The AUC values obtained after nasal delivery of solution, powder and microspheres were calculated as 13.24 ± 7.16, 11.40 ± 3.26 and 17.37 ± 7.85 mg/ml.min, respectively. High plasma concentration of the drug in 5 min was achieved with powder form and microspheres. It was emphasized that the plasma concentration–time profiles of three dosage forms were very close to the values in conventional oral treatment, and the plasma concentration of the drug was constant for several hours.

Tas *et al.* [68] compared solution, gel and lyophilized powder formulations of MTC using carbopol polymer and these were compared *in vitro*, *ex vivo* and *in vivo*. In contrast to *in vitro* and *ex vivo* results, nasal *in vivo* absorption of MTC from gel is higher than those of other formulations. In another study by the same group of researchers, sodium carboxymethyl cellulose and hydroxypropyl-β-cyclodextrin (HP-β-CD) were used as mucoadhesive polymer and permeation enhancer, respectively [69]. The histological studies demonstrated that solution and gel formulations do not lead to severe damage to the mucosa. In the *in vivo* studies on sheep, the highest relative bioavailability as compared with oral solution was achieved with gel, whereas the lowest bioavailability was with solution. On the other hand, HP-β-CD increased the bioavailability of MTC from the powder formulation and decreased irritation on the nasal mucosa. In the literature, the permeation-enhancing mechanism of HP-β-CD has been explained in detail [47].

The studies in which microspheres of MTC were prepared with different polymers for nasal delivery are summarized below. In these studies, microspheres were obtained by using the spray-drying method. It is easy and reproducible to obtain microspheres [70]. In preparation of microspheres of MTC, chitosan and its derivative, sodium alginate and gellan gum were used as polymers. Chitosan is extremely effective in the passage of particularly hydrophilic drugs through nasal mucosa [78-80]. This effect was associated with its mucoadhesive characteristic and its ability to transiently open tight junctions in mucosa [81,82]. It was also demonstrated that chitosan does not lead to any histological changes in nasal mucosa [81]. The strong mucoadhesive characteristic of chitosan has been attributed to ionic interaction of positive-loaded amino groups of the D-glucosamine unit in its structure with negative-loaded sialic acid groups of

mucin or with other negative-loaded groups of the mucosal membrane [83,84].

In a study, microspheres of MTC were prepared using chitosan and sodium alginate [71]. Microspheres had high encapsulation efficiency (83 – 97%) and a strong mucoadhesive property. The permeation of MTC through sheep nasal mucosa from microspheres containing chitosan and sodium alginate/chitosan mixture was significantly higher than those with sodium alginate. This was explained with the permeation-enhancing effect of chitosan. In another study, 5-methylpyrrolidinone chitosan was synthesized to enhance mucoadhesiveness of chitosan, and microspheres of MTC were prepared with this polymer [72]. The mucoadhesion capacity of the microspheres prepared with 5-methylpyrrolidinone chitosan was found to be significantly higher than those with chitosan.

MTC-loaded microspheres were prepared using gellan gum [73]. The mucoadhesion of microspheres increased as the polymer concentration increased. It was noted that polyanion polymers were more bioadhesive than the polycation or nonionic polymers [85,86]. The microparticles prepared ensured extended release for 5 h. The drug substance release rate and amount decreased as the gellan concentration increased. It was identified that the gellan microparticles prepared did not lead to any damage to the epithelial tissue.

5.2 Ondansetron

In the prevention of adverse effects, such as nausea and emesis that are associated with anticancer treatment, the serotonin (5-hydroxytryptamine) subtype-3 (5-HT_3) antagonists are used to improve the patient's quality of life [1,2]. OND is one of the selective 5-HT_3 receptor antagonist used in the prevention of nausea and emesis occurring due to chemotherapy, radiotherapy applications and postoperation [87,88]. The oral bioavailability of OND is about 60% due to the hepatic first-pass effect [89]. In addition, it undergoes intestinal metabolism such as intestinal secretion with CYP3A4 and P-glycoprotein [90]. Oral tablets (4 or 8 mg), fast-dissolving tablets (4 or 8 mg) and oral solution (4 mg/5 ml) and i.v. solution (2 mg/ml) of OND are commercially available. Due to the previously reported disadvantages of oral and i.v. delivery of antiemetics, alternative delivery routes for OND have been studied. Transdermal [91-94] and nasal routes [95-101] are the most attractive routes. Besides, colon delivery of OND was investigated [102].

There are *in situ* gel-forming solutions and microparticulate systems of OND for nasal delivery in the literature. In these formulations, Pluronic 127, chitosan, gellan gum, poly-L-lactide and poly(D,L-lactide-co-glycolide) (PLGA) as polymers and CDs as permeation enhancer were used. The first nasal application of OND was studied by Hussain *et al.* [95]. The absorption of nasal solution of OND was compared with the i.v. administration. For the nasal application, a special surgical procedure was used to ensure maintenance of drug solution in the nasal cavity. OND was rapidly and easily absorbed from the nasal rat mucosa. C_{max} was achieved in a very brief time such as 10 min. Oral preparation of OND should be given to patients 30 min prior to chemotherapy [89]. Therefore, nasal delivery of OND could be considered as a good alternative to the oral route. This study is important in that the fast and complete absorption of OND through nasal mucosa was shown for the first time.

In the other study, nasal solution of OND was prepared with sulfobutylether-β-cyclodextrin sodium salt (SB-β-CD) and DM-β-CD was used as a permeation enhancer [96]. The preliminary studies demonstrated that permeation of OND through nasal mucosa is very fast and lag time was not observed, and an increase in the drug concentration improved the *in vitro* permeation rate of OND. SB-β-CD and DM-β-CD enhanced the solubility and stability of OND. *In vivo* efficiency of the formulation containing SB-β-CD, PEG 300 and benzalkonium chloride was compared with oral and i.v. applications in rats. The nasal solution increased the $AUC_{(0-2\ h)}$ and C_{max} values of the OND by 2.1- and 1.7-folds respectively, as compared with oral delivery.

As mentioned above, *in situ* gels have superiority in terms of nasal delivery of drugs. Nasal *in situ* gels of OND was reported in the literature [97]. In this study, Pluronic 127 and hydroxypropyl cellulose were used as thermosensitive polymer and mucoadhesive polymer, respectively. The increase in the concentration of hydroxypropyl cellulose enhanced mucoadhesiveness of the gel while decreasing its spreadability properties. Further, *in vitro* diffusion studies demonstrated that OND release from gels was affected by the viscosity of the vehicle.

One of the current strategies to improve bioavailability of nasally delivered drugs, as mentioned previously, is to develop microparticulate systems in which mucoadhesive polymers are used. Therefore, microspheres of OND were prepared with different polymers (chitosan, poly-L-lactide, PLGA and gellan gum) [98-101]. In these studies, a spray-drying method was used for the preparation of microspheres.

Gungor *et al.* [98] prepared cross-linked chitosan microspheres of OND with glutaraldehyde at various concentrations. OND-loaded chitosan microspheres were positively charged. It has been emphasized that the positive charge of microspheres interact with the negative-charged nasal mucosa, thus enhancing the mucoadhesive property of the microspheres and extending residence time of the drug in the mucosa [83]. I.v. solution and nasal solution of OND and cross-linked chitosan microspheres (F2, F3 and F4) were administered to rats at 2 mg/kg. Plasma OND concentration profiles as a function of the time are given in **Figure 2**. In 10 min following delivery of i.v. and nasal solutions, the OND plasma concentrations were found to be 0.64 ± 0.12 and 0.45 ± 0.20 μg/ml and $AUC_{0-\infty}$ values as 0.49 ± 0.20 and 0.35 ± 0.09 μg.h/ml, respectively. Hence, there was no statistically significant difference between the two application routes (see insert graph in **Figure 2**).

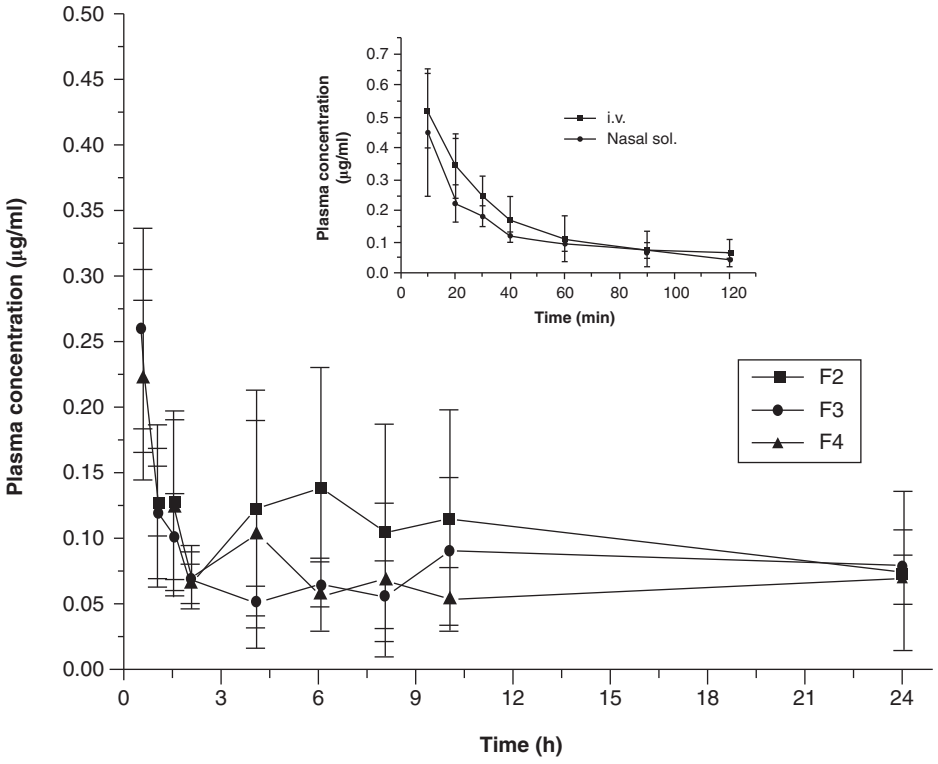

Figure 2. Plasma levels of ondansetron (OND) in rats after application of nasal OND-loaded microspheres (inset graph: Plasma levels of OND in rats after i.v. and nasal applications of OND solution). The dose of OND was 2 mg/kg for both i.v. and nasal route. Each point represents mean ± SD (n = 4 – 5).
Reprinted with permission from [85,98], Informa Healthcare.

$AUC_{0-\infty}$ values obtained from F2, F3 and F4 microspheres were calculated as 4.97 ± 3.15, 4.44 ± 0.65 and 4.03 ± 2.24 µg.h/ml, respectively. There was no statistically significant difference between the microspheres, in terms of both C_{max} and $AUC_{0-\infty}$. Plasma OND level was sustained for 24 h following nasal delivery of microspheres. However, both i.v. and nasal OND solutions were effective for only 2 h. This study has demonstrated that chitosan-based microspheres can be considered as a nasal drug vehicle system for OND. The effect of chitosan to enhance permeation of drugs in nasal formulations through the mucosa has been mentioned previously.

Microspheres prepared with polyester polymers provide prolonged drug release. The particulate systems prepared with this polymer are also evaluated as a nasal drug vehicle system. Poly-L-lactide and PLGA polymers are Food and Drug Administration (FDA) approved, biocompatible and biodegradable polyester polymers. Gungor *et al.* [99] prepared OND microspheres using these polymers. The effects of the solvent type (dichloromethane and dichloromethane–ethyl acetate mixture) and polymer type (poly-L-lactide and PLGA on *in vitro* characterization of microspheres were evaluated. *In vitro* OND release from microspheres continued for 96 h. The type of the solvent used did not have any effect on drug release from microspheres prepared with PLGA. However, drug release from poly-L-lactide microspheres prepared with dichloromethane was slower than that of those prepared with dichloromethane–ethyl acetate. The microspheres prepared with dichloromethane–ethyl acetate and PLGA were nasally delivered to rats. Plasma OND level (30 – 48 ng/ml) remained relatively constant for a very long time (96 h).

Mucoadhesive OND microspheres were prepared with gellan gum at various concentrations [100]. An increase in polymer concentration enhanced mucoadhesion without any significant effect on drug release rate and amount. Drug release from microspheres was extended up to 5 h. The microspheres prepared did not cause any damage to epithelial cells. The same researchers also studied *in vivo* nasal absorption of OND from gellan microspheres [101]. Following i.v., oral and nasal delivery, the $AUC_{0-\infty}$ values were calculated as 71.59 ± 8.93, 28.64 ± 3.88 and 46.05 ± 1.84 ng/ml.min, respectively. The corresponding data indicated that drug absorption from nasally delivered microspheres was higher than that of oral administration.

5.3 Granisetron

GRN hydrochloride was used in the treatment of chemotherapy-, radiotherapy-induced and postoperative nausea and emesis. GRN, a type of selective 5-HT_3 receptor antagonist,

is effective and well tolerated in adult and pediatric patients [103]. Its oral tablets (1 or 2 mg) and i.v. solution (1 mg/ml) are commercially available. Following oral delivery, GRN reaches C_{max} in 3 h. It should be administered an hour prior to chemotherapy treatment. Therefore, the nasal route may be a potential alternative route for GRN. In recent years, there have been studies on its delivery by nasal [104,105] and transdermal [106,107] routes. Furthermore, the transdermal preparation of GRN was approved by the FDA in 2008.

Woo [104] performed the first studies on nasal administration of GRN. In the study, GRN was applied nasally or intravenously to rats at the same dose (6 mg/kg). The $AUC_{0-\infty}$ values obtained after i.v. and nasal delivery of GRN were 609.5 ± 6.6 and 603.2 ± 47.2 ng.h/ml, respectively. These findings demonstrated that GRN, in a similar way to OND, is well absorbed through nasal mucosa, and its nasal bioavailability is comparable with i.v. delivery.

In another study, GRN microparticles were prepared with a freeze-drying method. HP-β-CD and sodium carboxymethyl cellulose were used as permeation enhancer and polymer, respectively [105]. The release amount of GRN from microparticles was found to be higher than that of the pure drug. Additionally, GRN microparticles had significantly lower cytotoxicity and higher permeation (2.48-folds) compared with pure GRN. The increase in drug permeation was explained by the high drug solubility due to the synergic effect of sodium carboxymethyl cellulose and HP-β-CD. Furthermore, the increase in bioavailability of GRN was associated with the bioadhesive property of sodium carboxymethyl cellulose and thus increased residence time of drug in the nasal mucosa. Based on these results, the authors suggested that intranasal delivery system could be a potential alternative for oral and i.v. administrations of GRN.

As can be seen in the studies mentioned above, GRN is a good candidate for nasal delivery. Hence, Phase II studies of intranasal GRN formulation, which was developed by Ship Nippon Biomedical Laboratories in the USA, are continuing [108]. It is expected that nasal formulations of GRN will be on market soon.

5.4 Dimenhydrinate

DMH is an over-the-counter drug, which is particularly used to prevent motion sickness. Its i.v. and i.m. injectable solutions (50 mg/ml), oral solution (12.5 mg/5 ml), oral tablets (15, 25 or 50 mg), chewable tablets (15 or 50 mg) capsules (25 or 50 mg) and rectal suppositories (25, 50 or 100 mg) are commercially available. It should be taken at least 30 min or preferably 1 – 2 h before traveling [54]. However, in cases of excessive nausea and emesis, it may be discharged before absorption. Alternative delivery routes to oral delivery are studied for DMH, as well.

In a study on nasal delivery of DMH, a nasal solution formulation was prepared by using gellan polymer [109]. Thiolization procedure was applied to enhance mucoadhesiveness of gellan. The mucoadhesion strengths of formulations prepared with thiolated and non-thiolated polymer were measured, and the thiolated polymers were found to be more mucoadhesive. The histopathological evaluation demonstrated that the formulation with thiolated gellan gum leads to little erosion along the nasal epithelium. Furthermore, the vascularization was increased in the basal membrane and superficial section of the mucosa to which the formulation was administered. This finding was associated with the mucoadhesion of the thiolated gellan gum and its ability to enhance permeability. *In vitro* drug permeation studies conducted with sheep nasal mucosa demonstrated that drug permeation significantly increases with thiolated polymer.

5.5 Domperidone

Domperidone (DOM) is a drug used in the prevention of emesis occurring due to various reasons. It is commercially available in rectal suppository (30 mg), oral suspension (1 mg/ml) and oral tablet (10 mg). However, its oral bioavailability is very low due to a hepatic first-pass effect (15%) [54]. Therefore, alternative delivery routes of DOM have been studied. DOM microspheres were prepared with the emulsification cross-linking technique for nasal delivery [110]. Starch was used as polymer and epichlorohydrin as cross-linker for preparation of microspheres. The microspheres were 22.8 – 102.63 μm in size and had good mucoadhesive and swelling properties. The drug–polymer concentration affected the *in vitro* release of the drug.

5.6 Promethazine

PRM is an antiemetic from the phenothiazine group, which is used in treatment of nausea and emesis associated with motion sickness or drug-induced and postoperative emesis [54]. It is commercially available as i.v./i.m. solution (25 or 50 mg/ml), oral syrup (6.25 mg/5 ml) and tablets (12.5, 25 or 50 mg) and rectal suppositories (12.5, 25 or 50 mg). Due to the disadvantages of oral and parenteral delivery, nasal systems of PRM have been developed as alternative delivery routes. Hafner *et al.* [111] prepared PRM microspheres with chitosan–ethyl cellulose at different ratios. *In vitro* extended drug release has been obtained with chitosan–ethyl cellulose microspheres at a ratio of 2:1.

In another study, microcapsule formulations using palm oil and sorbitan monooleate of PRM were developed [112]. The irritation potential of both microparticulate systems on the nasal epithelial tissue was evaluated *in vitro* and *in vivo*, with comparison with pure PRM. Pure PRM, when administered via nasal route to rats, causes a considerable local irritation on the nasal mucosa, while encapsulated PRM did not lead to any irritation.

6. Conclusion

Antiemetic drugs are extensively used in a special patient group, particularly for the treatment of nausea and emesis occurring after cancer chemotherapy and radiotherapy.

Therefore, they have an important role in improving the quality of life of patients. Commercial preparations of these drugs are frequently delivered by i.v. and oral routes in the current treatment. However, there are some limitations in terms of bioavailability and patient compliance related to oral and parenteral administration of antiemetic drugs. Therefore, a considerable amount of study has been performed to develop alternative delivery routes of antiemetic drugs. Among the alternative routes, nasal one offers unique advantages with fast and high drug absorption and high patient compliance. The research studies undertaken indicate that nasal formulations of antiemetics have superiorities over the oral route in terms of bioavailability. Antiemetic drugs, particularly MTC, OND and GRN, can be considered as ideal candidates for nasal delivery.

7. Expert opinion

In drug delivery, patient compliance is very important for the effectiveness of the treatment. In general, oral preparations are the most preferred forms by the patients; however, nausea and emesis is an important issue in oral delivery of antiemetics. There are limitations in the patient's compliance to treatments and thus in effectiveness of the conventional drug delivery. Therefore, it is important to develop novel delivery systems as an alternative to oral and parenteral preparations of antiemetic drugs, which are frequently used by patients undertaking cancer treatment.

Nasal delivery, which is a non-invasive application, can be considered as an alternative in this respect. The nasal route has certain superiorities including overcoming hepatic first-pass effect, fast and high drug absorption due to its thin membrane structure and wide blood vessel network, and good patient compliance.

The MW of the drug is an effective parameter for passage of drugs through the nasal mucosa. The antiemetic drugs investigated for nasal delivery and reviewed in this article have relatively small MW with < 500 Da and, therefore, they can be considered as good candidates for nasal transport. Also the hydrophilic or lipophilic characteristics of drugs are just as important as the MW in passage through the mucosa. Drug passage through nasal mucosa usually takes place via the transcellular and paracellular routes. While hydrophilic drugs prefer the paracellular route, lipophilic drugs pass through the transcellular route. Even if they have a similar MW, the amount of drug transport across the mucosa may not be the same due to different lipophilicity. In addition, nasal drug absorption is affected by the mucociliary clearance mechanism. With this mechanism, drugs are cleared from the nasal mucosa without achieving systemic effect. Different strategies have been evolved to overcome the limitation of the nasal route and/or to ensure the drugs pass the nasal mucosal barrier. These approaches include permeation enhancers [44-48] into formulations and using polymers that extend drug residence time in the mucosa. Another strategy is the use of mucoadhesive microparticulate systems [12,20,46,49] that extend the residence of drugs in the nasal membrane to improve permeability.

Several feasibility studies have been performed for nasal administration of MTC, OND, GRN, DMH, DOM and PRM. During recent years, these studies have primarily focused on MTC, OND and GRN. In these studies, it is noticeable that mucoadhesive polymer-based solution, *in situ* gel, mucoadhesive powder and microparticles have been optimized and evaluated by *in vitro/ex vivo/in vivo* studies. The plasma drug profiles obtained after nasal delivery of these formulations are significantly higher than those of the oral route. Therefore, it can be concluded that high bioavailability can be achieved by nasal administration of antiemetic drugs. The high bioavailability can be explained by the fact of the direct entering into systemic circulation of nasally delivered drugs without the hepatic first-pass effect and the long residence time of the formulations in the nasal mucosa and high localization of the drug in mucosa. Furthermore, the entrance of drugs into systemic circulation following nasal application is relatively faster than that of oral administration, which can be due to the thin structure of the nasal membrane and its extensive vascularization.

It is considered that nasal drug delivery systems can become a potential alternative and it is anticipated that nasal formulations of antiemetic can be on the pharmacy shelves in the near future to improve the quality of life of patients who suffer from nausea and emesis particularly during and after cancer chemotherapy.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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