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(REVIEW ARTICLE)

Ondansetron: A selective $5HT_3$ receptor antagonist and it advances in drug delivery system

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Abstract

Ondansetron is a serotonin ($5HT_3$) receptor antagonist used for the prevention and treatment of postoperative nausea and vomiting. It is available in many dosage forms in the market. Various analytical methods used for the determination of Ondansetron have been studied in this review article such as UV spectroscopy, mass spectroscopy, high-performance liquid chromatography, high-performance thin layer chromatography, a new electrospray ionization mass spectrometry etc. Ondansetron in human plasma can be estimated using this method. With time many advances have been made in the formulation aspects of Ondansetron, such as now a days it is available in floating drug delivery, transdermal as well as gastroretentive and orodispersible drug delivery system. New novel technologies are also mentioned in this review article related to 3D printing, nanofibers etc.

Keywords: Ondansetron hydrochloride; Gastro retentive floating tablet; Validation; Spectrophotometric; 3D printing

1. Introduction

Ondansetron hydrochloride is (RS)-9-methyl-3-[(2-methyl-1H-imidazole-1-yl)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one hydrochloride dehydrate. It belongs to the class of 5-HT_3 antagonists, which is commonly employed as an anti-emetic in combination with antiulcer and anticancer properties. It inhibits dopamine release, which leads to cell firing in the nucleus accumbens. In the peripheral nervous system, ondansetron also inhibits 5-HT_3 receptors, thereby blocking the depolarization of vagal afferent nerves and myenteric neurons, leading to an attenuation of 5-HT_3 receptor-mediated nociceptive response [1, 2].

Patients going through cancer chemotherapy radiation are suggested to consume ondansetron as it prevents nausea and vomiting. Earlier ondansetron was available only in oral dosage form, but with the advancement in formulation technology, it is available in various dosage forms to increase the bioavailability of the drug. Not to affect the gastro motility of the drug, researchers came up with gastro retentive, floating, transdermal and orodispersible drug delivery systems, and to get the faster onset of action intravenous drug delivery is also available. By the use of novel technologies, ondansetron is available in 3D printing and in nanofibers form [3, 1, 4].

To determine the ondansetron content in various dosage forms, different analytical methods such as UV spectroscopy, mass spectroscopy, high-performance liquid chromatography (HPLC) and high-performance thin layer chromatography (HPTLC) were used. These analytical methods were found to be simple, rapid, linear, accurate, precise and specific, hence can be successfully used for routine quality control analysis of ondansetron [5, 6, 7].

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Table 1 Analytical methods for the determination of Ondansetron

Analytical method	Sample	Method Development	Method Validation	Utility of Method	Ref
UV spectroscopy	Ondansetron HCL	Wavelength: 260- 288 nm Linearity range: 1-6 ug/ml	1. Accuracy: 95% ± SD 2. Precision: Intra-day: 0.7630 Inter-day: 0.6457 3. LOD: 0.38 ± 0.008 LOQ: 0.99 ± 0.018. 4. Recovery: 99.41 -100.43 %	This method was found to be simple, rapid, economical and acceptable for a wide linearity range	[7,8]
HPLC	20 tablets each containing 4 mg of Ondansetron HCl accurately weighed	Wavelength: 248 nm	1. Linearity: 10-60 ug/ml 2. R^2: 0.9982 3. Accuracy - 100.45% 4. Precision Intraday precision: 100.93 % ± 0.995 Interday precision: 101.75 % ± 1.052. 4. LOD: 1.005 ug/ml LOQ: 3.046 ug/ml 5. Robustness: % RSD 2.674 ± 0.081	The method is reliable and accurate therefore it can be successfully applied for the routine quality control analysis of Ondansetron hydrochloride in the tablet dosage form	[5]
HPTLC	Ondansetron HCl	Wavelength: 254 nm Spot concentration on TLC plates: 200, 400, 600, 800, 1000 and 1200 ng/spot of ondansetron HCl respectively	1. Precision Intraday: 0.97-1.47% Interday: 0.69-0.77% 2. LOD: 14.83 LOQ: 44.92 ng 3. R^2: 0.9906 4. Recovery: 98.93 -101.16 %. 5. Robustness: % RSD 0.82 and 0.95.	The method can be used to determine the purity of the drug by analysing it for related substances and impurities.	[9]
Mass spectroscopy method	Human plasma	Column: Gemini NX C18 analytical column (100·4.6 mm i.d., particle size 5 um) Method: Isocratic elution and an ion-spray voltage of +5500 V were applied. Mobile phase: Mixture of ammonium formate buffer (pH 3.0; 2 mM) and acetonitrile (30:70, v/v) Flow rate: 0.5 mL/min	Precision Intraday: 4.18% Inter day: 7.76%, 2. Stability Short term stability of Ondansetron: 7 h 10 min at ambient temperature. The long-term stability of Ondansetron: 06 days at 5 ± 3 °C. 3. Linearity: 5-100 ppm	The proposed method enabled the reliable determination of Ondansetron in bioequivalence study of ondansetron tablet. This method improves sensitivity, accuracy and Precision for the quantitative determination of Ondansetron in human plasma.	[6]

2. Different advances and formulation aspects of Ondansetron

2.1. Gastro retentive floating drug delivery system

2.1.1. Single-unit dosage forms

Low-density approach

A single-unit floating dosage form can be prepared using globular shells with a density lower than that of gastric fluid. These shells have been undercoated with sugar polymeric materials, including methacrylic polymer and cellulose

acetate phthalate. An additional layer of drug-polymer is then applied to these shells. The product floats on the gastric liquid and slowly releases the drug for a more extended period of time according to the type of release desired.

Fluid-filled floating chamber

The drug reservoir is covered with a microporous component with a gas-filled floatation chamber. The top and bottom walls of the device have an opening through which the GIT fluid enters to dissolve the drug. In order to prevent undissolved drugs from being left in the device, the side walls in contact with the fluid are sealed. This device should be swellable and contains a floatable fluid which is air, a gas, liquid, or solid, with appropriate specific gravity and inert. A float remains within the water as long as the device is submerged. The drug is released from the stomach slowly, the shell is disintegrated, and finally, it is expelled from the body through the intestine [10].

Multiple-unit dosage forms

In order to develop a reliable formulation with all the advantages of a single-unit dose form, it is necessary to design multiple-unit dosage forms. A number of polymers, including albumin, gelatin, starch, polymethacrylate, polyacrylamine and polyalkylcyanoacrylate have been used in the manufacturing of microspheres due to their high loading capacity. Microsponges made from polymeric materials, also called microballoons, have been prepared. Excellent *in vitro* floatability is demonstrated by microspheres, which have a characteristic hollow internal structure. In carbon dioxide-generating multiple-unit oral formulations, several devices have been described that extend, unfold, or erect due to carbon dioxide generated in the devices after administration. When these dosage forms exceed a diameter of 12-18 mm in their expanded state, they are excluded from passing through the pyloric sphincter [11].

Table 2 Marketed products of gastroretentive drug delivery system

Brand Name	**Delivery System**	**Drug(dose)**	**Company Name**
Valrelease®	Floating capsule	Diazepam (15 mg)	Hoffmann-LaRoche
Madorap® HBS (Prolopa® HBS)	Floating, CR cap	Benserazide (25 mg) and L-Dopa (100 mg)	Roche Products, USP
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India
Topalkam®	Floating liquid alginate preperation	Al-Mg antacid	Pierre Fabre Drug, France
Conviron®	Colloidal gel forming FDDS Bilyer floating capsule	Ferrous Sulphate	Ranbaxy, India
Cytotech®	Bilayer Floating Capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1 gm)	Ranbaxy, India

2.2. Transdermal drug delivery system

It is poised to provide a viable alternative to hypodermic injection and an attractive alternative to oral drug delivery. The use of topical formulations to treat local indications has been developed for hundreds of years. It was approved in the United States in 1979 to deliver scopolamine for three days as a systemic delivery system. It took a decade for nicotine patches to become the first transdermal blockbuster, which raised the profile of transdermal delivery in medicine. In addition to transdermal delivery systems for drugs such as estradiol, fentanyl, lidocaine and testosterone, there are also combination patches containing two or more drugs, including iontophoretic and ultrasonic delivery systems for analgesia [12].

Table 3 Transdermal drugs approved by the US FDA

Approval year	Drug	Indication	Product Name	Marketing company
1979	Scopolamine	Motion sickness	Transderm-Scop	Novartis Consumer Health (Parsippany, NJ)
1981	Nitroglycerin	Angina pectoris	Transderm-Nitro	Novartis (East Hannover, NJ)
1984	Clonidine	Hypertension	Catapres-TTS	Boehringer Ingelheim (Ridgefield, CT)
1986	Estradiol	Menopausal symptoms	Estraderm	Novartis (East Hannover, NJ)
1990	Fentanyl	Chronic pain	Duragesic	Janssen Pharmaceutica (Titusville, NJ)
1991	nicotine	Smoking cessation	Nicoderm, Habitrol, ProStep	GlaxoSmithKline (Philadelphia, PA), Novartis Consumer Health (Parsippany, NJ) Elan (Gainesville, GA)
1993	Testosterone	Testosterone deficiency	Testoderm	Alza, Mountain View, CA
1995	Lidocaine/epinephrine (iontophoresis)	Local dermal analgesia	Iontocaine	Iomed (Salt Lake City, UT)
1998	Estradiol/norethidrone	Menopausal symptoms	Combipatch	Novartis (East Hannover, NJ)
1999	Lidocaine	Post-herpetic neuralgia pain	Lidoderm	Endo Pharmaceuticals (Chadds Ford, PA)
2001	Ethinyl estradiol/norelgestromin	Contraception	Ortho Evra	Ortho-McNeil Pharmaceutical (Raritan, NJ)
2003	Estradiol/levonorgestrel	Menopausal symptoms	Climara Pro	Bayer Healthcare Pharmaceuticals (Wayne, NJ)
2003	Oxybutynin	Overactive bladder	Oxytrol	Watson Pharma (Corona, CA)
2004	Lidocaine (ultrasound)	Local dermal anesthesia	SonoPrep	Echo Therapeutics (Franklin, MA)
2005	Lidocaine/tetracaine	Local dermal analgesia	Synera	Endo Pharmaceuticals (Chadds Ford, PA)
2006	Fentanyl HCl (iontophoresis)	Acute postoperative pain	Ionsys	Alza, Mountain View, CA
2006	Methylphenidate	Attention deficit hyperactivity disorder	Daytrana	Shire (Wayne, PA)
2006	Selegiline	Major depressive disorder	Emsam	Bristol-Myers Squibb (Princeton, NJ)
2007	Rotigotine	Parkinson's disease	Neupro	Schwarz Pharma (Mequon, WI)
2007	Rivastigmine	Dementia	Exelon	Novartis (East Hannover, NJ)

2.3. Intravenous delivery

Oral and intravenous administration of ondansetron is available, in both cases the base form of the compound is used i.e. hydrochloride dihydrate. Oral preparations can be co-administered with food as they do not have any significant effect on absorption. The intravenous preparation is an isotonic aqueous solution that has been buffered to a pH of 3.5 with sodium citrate and citric acid monohydrate. It is administered either by slow intravenous injection or by intravenous infusion over a period of minutes. Ondansetron is usually administered orally for prophylaxis and treatment of chemotherapy-induced vomiting. Ondansetron is indicated for the prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of postoperative nausea and vomiting (PONV). Eg Zofran® Injection, Ondansetron 2 mg/ml solution for injection [3].

2.4. Orodispersible drug delivery

Orally disintegrating tablets are prepared using several technologies such as freeze drying, tablet molding, direct compression, spray drying, and sublimation. Tablets can be manufactured easily and economically using direct compression. These methods are advantageous because of their conventional equipment, commonly available excipients, and the limited number of processing steps involved. Disintegration and solubilization of a directly compressed tablet are controlled by a combination of disintegrants, water-soluble excipients, and effervescent agents working individually or together. A few of the most commonly used superdisintegrants are croscarmellose sodium (cross-linked carboxymethylcellulose), crospovidone (cross-linked povidone) and sodium starch glycolate. It is important to note that the addition of superdisintegrants is the major factor affecting the rate at which orally disintegrating tablets disintegrate and dissolve in simulated media. A combination of water-soluble excipients and effervescent agents further accelerates the disintegration process [1].

3. Novel technologies used in the formulation of Ondansetron dosage forms

3.1. 3D Printing

Ondansetron is an anti-emetic drug, commercially available as soluble films or orally disintegrating tablets as it has low solubility which may induce vomiting. However, the bitter taste of Ondansetron is still an issue. The solution of ondansetron has made use of various taste-masking strategies like sweeteners, ion-exchange resins, etc.

Three-dimensional printing (3DP) is a technology adapted for the preparation of dose print lets (3D printed tablets). This technique includes various technologies, of which, the majority have been used in the pharmaceutical industry like powder bed inkjet printing, fused deposition modeling, semisolid extrusion, selective laser sintering, direct powder extrusion and stereolithography 3D printing, the biggest advantage is the speed at which parts are produced compared to traditional manufacturing approaches. With the CAD model, intricate designs can be uploaded and printed in a few hours. Additionally, 3D printing allows for rapid concept development and verification. With additive manufacturing, today a prototype can be made in a matter of hours rather than days or weeks like it used to take earlier. The ability to produce functional end parts in low- to mid-volumes offers a huge advantage over traditional manufacturing methods, despite the fact that industrial additive manufacturing machines generally require more time for printing and post-processing parts [4].

3.2. Nanofibers

Ondansetron is an agent widely administered to relieve nausea and vomiting which are the common complication after surgery. The aim is to design and evaluate the physicochemical and clinical effects of the fast-dissolving nanofiber of ondansetron whose potential effects were expected to be enhanced effectiveness, bioavailability and patient compliance. Nanofibers can be prepared using the electrospinning method where polyvinyl alcohol and alpha-cyclodextrin are used as polymer and sodium saccharin as a sweetener. Possessing a mean diameter of 159 to 30 nm, the fast-dissolving nanofiber shows the almost same anti-emetic effect as that of an orally disintegrating tablet.

Table 4 Recent patents

Patent no	Title	Formulation	Manufacturing process	Inventors	Applicant	Claims	Ref
TW200528100A	New polymorphic forms of ondansetron, processes for preparing them, pharmaceutical compositions containing them and their use as antiemetics	Injection	a) Ondansetron HCl dissolved in a mixture of Ci-C3 alcohol and water b) Precipitating basic ondansetron by basifying the solution c) Filtering out the solid and washed with water d) Suspending the water-wetted solid obtained in stage c) in methanol with stirring under reflux and e) recovering the crystalline form.	Barjoan Pere Dalmases Carandell Lluis Sola Olle Francesc Xavier Alcobe Vallet Maria Cristina Puigjaner	Vita Cientifica SL	C-shaped polymorph of basic ondansetron, characterized by its X-ray powder diffraction pattern showing two unique peaks at 14.97 and 20.86 °20 and it does not show a peak below 6.5°20. The invention provides new stable polymorphic forms of ondansetron and processes for manufacturing them at an industrial scale so they have used c-shaped polymorph, E-shaped and D- shaped polymorph.	[13]
US10195139B2	Preparation for transnasal application	Trans nasal	Mention the manufacturing process used for manufacting of transnasal.	Ryoichi NagataShunji Haruta	Shin Nippon Biomedical Laboratories Ltd	A method for manufacturing a powdery formulation for nasal administration, comprises of a drug, and a carrier that comprises 1) a first crystalline cellulose 2) a second crystalline cellulose or a starch, and 3) tribasic calcium phosphate	[14]
AU2012216632B2	Crystallization Method and Bioavailability	Oral dosage form	Crystallization Method	Miranda CheneyMazen HannaRaymond K. HouckNing SHANDavid Weyna	Thar Pharma LLC	A composition comprising a physical mixture of zoledronic acid as a free acid and lysine in excess to the amount of zoledronic acid.	[15]
US7390503B1	Ondansetron orally	Orally disintegrating dosage	Freeze drying method was used to develop orally disintegrating ondansetron tablets,	Salah U. Ahmed Sudhir R. Gorukanti	Barr Pharmaceuticals Inc	A non-effervescent, orally disintegrating, a solid dosage form comprising:	[16]

	disintegrating tablets		which are bioequivalent to the existing Zofran orally disintegrating tablets.	Tahseen A. Chowdhury		ondansetron in a concentration of about 1 to about 10% by weight of said dosage form; mannitol (1% to about 60%), xylitol (1% to about 20%), crospovidone (1% to about 40%), microcrystalline cellulose (1% to about 10%) and a hydrophobic lubricant (up to about 10%) wherein said dosage form is not freeze-dried; and wherein the time taken for disintegration of the dosage form in water or in saliva is within 60 seconds.	
US20180028452A1	Antiemetic extended release solid dosage forms	Antiemetic extended release solid dosage forms	Because the internal portion consists of a non-covalently bonded matrix, the manufacturing process is a fundamentally two-step process of dry-blending and direct compression.	Reza Fathi Gilead Raday Patrick Gosselin Guy Goldberg	Redhill Biopharma Ltd	(1) a first dosage component comprising: a core comprising a non-ionic polymer matrix providing sustained release, a first amount of ondansetron or an equivalent amount of an ondansetron salt thereof dispersed within the matrix, and an electrolyte dispersed within the matrix; a first seal coat surrounding the core, the first seal coat comprising a non-ionic polymer matrix; and an immediate release drug layer surrounding the first seal coat, wherein the immediate release drug layer comprises a non-ionic polymer and a second amount of ondansetron or an equivalent amount of an ondansetron salt thereof dispersed therein; and (2) a second dosage component comprising: a core comprising a	[17]

						third amount of ondansetron or an equivalent amount of an ondansetron salt thereof, at least one filler, and a lubricant; and a coating surrounding the core, the coating comprising water and a mixture of methacrylic acid-alkyl acrylate copolymers with alkaline groups.	
EP1970055B1	Multi-layered tablet with triple release combination	Multi-layered tablet with triple release combination	The tableting machine used for manufacturing of multi-layered tablets of the invention had two powder filling positions and one internal core dispenser/centering device, such as for example the Fette machine model 4090, Kilian-Centra-Cota kind or Korsch-Central Core Coater 3C. These machines are able to take said cores, place and center them correctly into the die where the granulate is filled for the partial coating of said core. The dispenser can be adapted to dispense different dosage forms.	Fernando G. Toneguzzo Glenn A. Meyer Marcelo A. Ricci Marcelo A. Coppari Ana C. Pastini Gustavo A. Fischbein	Osmotica Kereskedelmi es Szolgaltato KFT	A combination release tablet comprising: a) a drug-containing rapid release first compressed composition comprising at least one drug; b) a drug-containing extended release second compressed composition comprising at least one drug and a release rate modifier; and c) a preformed and film-coated extended release intermediate drug-containing composition comprising a drug-containing core surrounded by a coating; wherein the first compressed composition and second compressed composition oppose one another, are in direct contact with, in stacked arrangement with respect to, and disposed on opposite faces or surfaces of the intermediate drug-containing composition, whereby the tablet provides three different active agent release profiles.	[18]

4. Results and discussion

The study's main purpose was to understand the various advances in the drug delivery system of Ondansetron – a selective $5HT_3$ receptor antagonist. From this study we have understood the various new formulation of ondansetron which helps to increase the therapeutic effect of it, such as gastro retentive floating drug delivery system where the drug does not affect the gastric motility, transdermal drug delivery system, by using intraveneous infusion of ondansetron an intractable vomiting, a rare event can be treated. We also get to know the novel technologies used to deliver ondansetron such as 3D printing and nanofibers.

Future scope

In the 1980s, ondansetron was introduced into clinical practice and was widely accepted antiemetic of choice for prevention and treatment in the 1990s. As a result of anesthesia and surgery, nausea and vomiting are common in cancer treatment. As a result of basic science research and subsequent clinical development that demonstrated superior efficacy, safety, and pharmacoeconomic profile, ondansetron secured its enviable position in the market. Further challenges include anticipatory vomiting in cancer treatment and the need for a "rescue" antiemetic in patients who undergo surgery. Thus, new directions in research should be pursued as part of the investigate other non-conventional uses of ondansetron in clinical settings practicing.

5. Conclusion

The anti-emetic, Ondansetron hydrochloride was previously available only as an oral formulation. This review article is a combination of the old and new technologies. Ondansetron has been a part of, like the gastro retentive floating drug delivery system, transdermal drug delivery system, and intravenous infusion. Techniques like 3D Printing and nanofibres have been the most important novel systems. The effects of these advances were found to be enhanced effectiveness, bioavailability and patient compliance. To conclude, in order to avoid effects like nausea and vomiting more efficiently in treatments like cancer, it is necessary that the different novel technologies are studied and implemented.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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