INTRODUCTION
Respiratory system is commonly infected with influenza viruses [1] and mainly orthomyxoviridae family (A, B, C). Worldwide, 2.5–5 hundred thousand people were reported death and 3-5 million diagnosed with acute illness [2] annually. Viruses classified with respect to activity of glycoproteins neuraminidase (N/NA), hemagglutinin (H/HA) and M2 ion channel. Influenza A and B are seasonal influenza with different subtypes such as H1–H16 (16 hemagglutinin) and N1–N9 (9 neuraminidase). Well-known viruses H1N1 and H3N2 are generally subtyped of seasonal virus (Influenza A). The avian influenza virus H5N1 [3–5] have great interest among the people but swine influenza (novel H1N1) is completely different from seasonal H1N1 influenza virus [6]. In the 20th century, 20–50 million people from different countries were killed with Spanish flu, 1–2 million from Asian flu, and 7 hundred thousand from Hong Kong flu [7, 8]. Virus infection was initiated by hemagglutinin after binding with a receptor called Sialic acid, 1 (fig. 1). Then other cells infected by new viruses with the help of neuraminidase [9, 10]. Life threat influenza can only be overcome with annual immunization. However, the limitation related to efficacy, timeline and design of the vaccine production increase the need for antiviral drugs. The approved antiviral drugs M2 ion channel and NA inhibitors are the basic option for therapeutic treatment with prevention. This classification based on resistance behavior, tolerance study, pharmacokinetics and drugs mechanism of action [11–17].

Neuraminidase inhibitors
Proteins (H and N) are available on the walls of influenza virus surfaces. New viral molecule was released by host cell due to enzymatic function of neuraminidase, will help to catalyzed glycoside hydrolysis. As a result, α-ketosidically connected sialic acid with glycolipid, glycoprotein, and hemagglutinin divided increased infectious molecule. However, the nascent virus is still securing with host cell due to an interaction between HA/HA receptor. The viral molecule exhibit HA/HA receptors on the surface, which enables new molecules stick together. The viral particles emerged from the clump and host cell when neuraminidase receptor removed sialic acid. In the respiratory, glycosylated components are digested by neuraminidase, contribute viral infection. Therefore, design-based modern drug act on the site of neuraminidase inhibitors, depend on its clinical efficacy, mechanism, genetic role are the key feature for success [18–20]. The neuraminidase inhibitors prompt action and excellent mortality is the main reason for its demand [21, 22]. The drugs and their pharmaceutical formulations worked for the treatment of deadly disease are Oseltamivir 2, Laninamivir 3, Zanamivir 4, Peramivir 5 [23–25] (fig. 1), established on sialic acid transformation [26–28]. Influenza experts from different countries set up a neuraminidase inhibitors susceptibility network (NISN) for the outcome of clinical result and monitoring development process. This committee is participating to monitor liability studies for encouraging the people to know the exact method of evaluation and investigation process to control influenza virus.
M2 ion channel inhibitors

Amantadine 6 and Rimantadine 7 (fig. 2) licensed by United States of America (USA) in the years 1966 and 1993 respectively for the treatment of influenza A as M2 ion inhibitor. Allosteric inhibition controls the movement and activity of M2 by the presence of methyl group in amantadine; consequently, it blocks the release of RNA. It was found that M2 ion is successful for influenza A but ineffective towards influenza B. Therefore, these drugs are precise only for influenza A. M2 inhibitor has extraordinary response to antibiotic resistance [29, 30], but it is very less compared to neuraminidase inhibitors [31, 32]. Through endocytosis process, host cell allows viruses to enter. At low pH, M2 channel permits the virus to viral interior due to an activity of endosome responsible for maturation and growth of molecule. The reproduction is continued in cytoplasm, viral ribonucleic acid (RNA) and genetic material released from protein matrix [33]. Therefore, it is very important to develop inhibitors functioning against the virus but in native condition.

Peramivir

Peramivir is a predominant cyclopentane based neuraminidase inhibitor. The binding capacity of the inhibitor will be half (IC50) with a concentration in the range 0.09–1.39 nM and 0.6–10.8 nM respectively for influenza A and B strains. This value is for Oseltamivir carboxylate 0.01–2.24 nM, 6.39–24.3 nM and for Zanamivir 0.30–2.32 nM, 1.53–17.0 nM [45]. The drug is productive without any complication for seasonal influenza viruses [46]. The Peramivir IV was first launched with trade name Rapiacta in Japan (2010). The drug prescribed for acute treatment in adults is 300 mg daily but for severe cases, hospitalized patients, 600 mg daily dose is recommended. The drug eliminated through renal and not metabolized in the human liver.

Biotransformation

Oseltamivir

Oseltamivir phosphate 8 is significant ester prodrug, applied orally for prevention and curing of influenza disease (A and B). It’s brand name Tamiflu is available in quantity of 75 mg. The approved regimen for adults is 75 mg daily two times for 5 d with respect to influenza (A and B), but it is different for the prophylactic regimen. For control and prevention, daily dose is 75 mg once; for a minimum of 10 d up to 42 d. The intake dose for healthy participants follows linear pharmacokinetics in the range of 75–675 mg [34–36]. Oseltamivir is absorbed in the gastrointestinal tract then metabolized and converted into Oseltamivir carboxylate 9 (fig. 3) in the liver and later on, uniformly distributed in the body. After oral administration, therapeutic action continues for 30 min with the metabolite (80%) but the remaining 20% available 3–4 h in plasma. The drug half-life is 1.8h. It was found that renal disease may affect active metabolite clearance and found that cytochrome P450 has only 3% interaction with plasma protein. Similar action occurs during glucuronosyl transferases [37–38].

Laninamivir

Laninamivir octanoate is an inactive prodrug and the commercially approved product (inavir) is available in Japan since 2010 [49]. Single dose of Laninamivir octanoate hydrate is limited to children with age above 10 y is 40 mg and below 10 y is 20 mg. Laninamivir, active metabolite of Laninamivir octanoate (LO) formed within 24 h due to hydrolysis in the octanoyl ester site. When LO is mixed with water in the human body, equilibrated to form 3-acetyl form 10, 2-acetyl form 11 (fig. 4) known as major and minor metabolites [50].

Zanamivir

Relenza is the trade name of Zanamivir, an anti-influenza inhibitor, which obtained the regulatory approval in 1999. It targets respiratory site and available as inhaled powder. The pharmaceutical formulation has high potential against people diagnosed with deadly disease influenza A (H5N1). The maximum amount of 20 mg (10 mg twice) is allowed daily as inhalation, continued for 5 consecutive days. However, for prophylaxis, time and quantity limit is 10 mg daily for 28 d for children age five or more, and same for adults [39–40]. The nasal spray set down into posterior nasal and nostril approximately 88% but 13% in lung, 78% in oropharynx deposited active site for replication of influenza virus [41]. Settle down in stomach (17%) and lung (2%) dose intake orally after fifty minutes [42]. Sputum and nasal wash sample resulted concentration about 50% inhibitory after 24 and 12 h, respectively [43] for healthy volunteers with 10 mg daily dose but 20 mg amount with infected sample quantified after 4 d [44]. The unchanged drug (90%) was found with excreted urine sample recommended without biotransformation [41]. Therefore, the drug not metabolized in the liver.
Amantadine

Amantadine is a very important drug as M2 proton channel inhibitor for influenza A. Symmetrel is the brand name normally used for amantadine. Its rate of absorption is high for young people compared to elder independents. Renal insufficiency does not appear to affect absorption, nor does the formulation used. First relative bioavailability studies of the oral administration reported that 86% recovery of the original dose (2–4 mg/kg) within 96 h from urine samples of five healthy men [51]. In case of ingestion after 72 h, 105 mg (52.5%) of the original dose was found in old man (84 y) urine [52]. Eight metabolites originated during metabolism. Besides the major metabolite produced by N-acetylation which is N–acytylelamantadine 12; other metabolites were observed. These are N–methylamantadine 13, N–dimethylamantadine 14, N–methylkneamantadine 15, N-formylamantadine 16, and metabolites 17, 18 and 19 (fig. 5) [53].

Fig. 5: Chemical structures of amantadine and amantadine metabolites

Rimantadine

Pharmaceutical formulation of Rimantadine is known as Flumadine. Recommended daily dose for adults is 200 mg for 11–42 d, for children of 1–9 y (5 mg/kg) 150 mg is the maximum limit. Several studies concluded that 10% of the amantadine dose and 75% of the Rimantadine dose are metabolized in the liver [54–57]. The metabolites are determined as free Rimantadine 7, m-hydroxyrimantadine 20, p-hydroxyrimantadine (equatorial 21 and axial 22) (fig. 6) [58–62].

Fig. 6: Chemical structures of m-hydroxyrimantadine (20) and the equatorial (21) and the axial (22) epimers of p-hydroxyrimantadine

Analytical techniques

UV-visible spectrophotometer

UV-visible spectrophotometer is a simple and common technique for quantification of pure, pharmaceutical formulations and biological fluids. First order derivative spectrophotometry applied for Oseltamivir capsules having sophisticated additional software for pharmaceutical industry [63]. The drug (λmax=217, 208.5 nm) is stable and suitable with different stress condition in dosage form [64, 65]. Potassium permanganate as oxidizing agent in alkaline medium, no interference from excipients for capsules [66]. The pure drug with formulation is determined by monitoring reaction mechanism in buffer medium with 4-chloro-7-nitrobenzo-2-oxa-1, 3-dioxide [67]. Zanamivir is evaluated in tablet formulation at 260 nm, validated respect to an international conference on harmonization guidelines [68, 69]. Amantadine derivative and ion pair complex was developed with 1, 2-naphtoquinone-4-sulfonate, bromoresol green (BGG), bromophenol blue (BPB), bromothymol blue (BTB) and methyl orange in pharmaceutical preparation and plasma samples [70–73]. Rimantadine can also be determined spectrophotometrically using 1, 2-naphtoquinone-4-sulfonic acid salt as derivatizing reagent in pharmaceutical dosage form [74].

High-performance liquid chromatography

High-performance liquid chromatography (HPLC) is an accurate instrument for pharmaceutical analysis. The inhibitor demand is increasing with time in the world because influenza viruses causes significant health alert. All determined drugs either applying ultraviolet detector or fluorescence detector. As well as used C18 and C4 column with a different manufacturer. The single mobile phase is usually a combination of two or more solvents. The ratio of the mobile phase is changed with time; gradient method investigation resulted in drugs with a short time. During the analysis buffer also added for the preparation of the mobile phase. Therefore, for the quantification of neuraminidase and M2 ion channel inhibitor, numerous HPLC methods are developed based on the mobile phase composition and the stationary phase for pure bulk drug, tablet dosage form and biological fluids (table 1) [75–102].

High-performance thin layer chromatography

Currently, the high-performance thin layer chromatography (HPTLC) has high demand because it involves fewer samples clean-up, high throughput value, low-cost methodology. The fundamental advantage of HPTLC leads to compute several samples at one time. Oseltamivir study performed on silica gel 60P–254 coated aluminum plate consists of mobile phase (toluene: methanol: ammonia=3.5:1.5:0.2, v/v/v), detected at Rf value (0.45±0.02) for bulk and its dosage form [103]. This technique applied to evaluate Zanamivir in a pharmaceutical formulation having a correlation coefficient close to one [90, 104].

Capillary zone electrophoresis

Capillary zone electrophoresis (CZE) is strong enough to large molecules additionally for small (organic/inorganic), separation technique controlled by electric field inside narrow bore capillaries. The method has several benefits with respect to fewer amounts of solvent, analyte and high resolution, applicable to forensic, environmental, clinical and pharmaceutical industry. It is a specific technique for the separation of the molecule along with enantiomers. The generic version of Oseltamivir was separated on fused capillary under potential (~15 kV) at room temperature. The analysis time is 1.5 min and detected at 226 nm included phosphate buffer [105]. Unmodified silica capillary, 4-methylbenzylamine in ethanol (20%) as background electrolyte, maintained+20 V for separation at 210 nm within 3 min in Rimantadine tablets [106]. Pharmaceutical products can be estimated with derivatization agent 1, 2-naphtoquinone-4-sulfonic acid by CZE in alkaline medium [107].
Table 1: Important parameters for the determination of drugs using HPLC

| Drug      | Mobile phase                                      | Stationary phase         | Flow rate (ml/min) | Detector (nm) | Application                          | Reference |
|-----------|--------------------------------------------------|--------------------------|--------------------|---------------|--------------------------------------|-----------|
| **Oseltamivir** | Acetonitrile: Methanol = 50:30, v/v | Purosphere C18 (250×4.6 mm, 5 μm) | 1.0                | 227           | API                                  | [75]      |
|           | Potassium dihydrogen orthophosphate (pH 3.2):    | YMC Pro C8 (150×4.6 mm, 5 μm) | 1.5                | 207           | Capsules                             | [76]      |
|           | Acetonitrile: Methanol = 60:20:20, v/v/v         | Water’s XBridge C18 (250×4.6 mm, 5 μm) | 0.9                | 226           | Bulk and pharmaceutical formulations | [77]      |
|           | Triethylamine (0.1%): Methanol = 60: 40, pH 10.04 with Conc HCl | | | | Bulk drug and capsules | [78]      |
|           | Phosphate buffer (0.02 M, pH 5 with 0.02 M TEA): Methanol = 50:50, v/v/v | Purosphere Star RP–18e (150×4.6 mm, 5 μm) | 1.5                | 215           | Bulk drug and capsules | [78]      |
|           | Mobile phase A–KH₂PO₄ buffer (0.05 m, pH 6): Acetonitrile = 90:10, v/v | ODS (50×4.6 mm, 5 μm) | 1.5                | 220           | Bulk drug                            | [79]      |
|           | Mobile phase B–KH₂PO₄ buffer (0.05 m, pH 6): Acetonitrile = 10:90, v/v | Gradient Programme | | | | |
|           | Ammonium acetate buffer (pH 6.9): Acetonitrile = 60:40, v/v | Purosphere C18 (250×4.6 mm, 5 μm) | 1.0                | 220           | Bulk drug and dosage                 | [80]      |
|           | Sodium acetate buffer (pH 4.5): Acetonitrile = 5:5:4, v/v | Phenomenex Luna C18 (250×5 mm, 5 μm) | 1.5                | 231           | Bulk and dosage form                 | [81]      |
|           | Acetonitrile: Nitric acid (10 mmol, pH 3): Acetonitrile = 60:40, v/v | Phenomenex C18 (250×4.6 mm, 5 μm) | 1.0                | λex 470       | Capsules and spiked plasma           | [82]      |
|           | Potassium dihydrogen orthophosphate (pH 3.5 with OPA): Acetonitrile = 5:0:50, v/v | Princeton Spher C18 (250×4.6 mm, 5 μm) | 1.0                | λem 541       | Pharmaceutical dosage form           | [83]      |
|           | Bicarbonate buffer (0.05 M, pH 10): Acetonitrile = 70:30, v/v | X-Terra RP18e (4.6×150 mm) | 1.0                | 220           | Pharmaceutical product               | [84]      |
|           | Mobile phase A: Triethylamine (0.2%, pH 3 with OPA) buffer | Kromasil C18 (250×4.6 mm, 5 μm) | 1.0                | 215           | Quality control sample               | [85]      |
|           | Mobile phase B: Acetonitrile Gradient programme | Oyster RP18e (250×4.6 mm, 5 μm) | 1.0                | 207           | Bulk and dosage form                 | [86]      |
|           | Potassium dihydrogen orthophosphate (0.05 mmol, pH 3 with OPA): Methanol: Acetonitrile = 60:25:15, v/v/v | Shimpack ODS (150×4.6 mm, 5 μm) | 1.6                | 215           | Human serum                          | [87]      |
|           | Phosphate buffer (0.05 M, pH 3) with triethylamine (1 ml/l): Acetonitrile = 70:30, v/v | Zorbax CN (150×4.6 mm, 5 μm) | 1.2                | 226           | Capsule                              | [88]      |
|           | Formic acid (0.04 M, pH 3 with NaOH): Methanol = 50:50, v/v | Sunfire C18 (4.6×250 mm, 5 μm) | 1.0                | 285           | Tablet dosage form                   | [89]      |
| **Zanamivir** | Methanol: Water = 95:5, v/v | Phenomenex RP C18 (250×4.6 mm, 5 μm) | 1.0                | 230           | Bulk and capsule                     | [90]      |
|           | Phosphate buffer (0.02 M, pH 5): Methanol = 50:50, v/v | Agilent zorbax eclipse C18 (150×4.6 mm, 5 μm) | 0.5                | 230           | Tablets                              | [91]      |
|           | Potassium dihydrogen orthophosphate (pH 4): Acetonitrile = 40:60, v/v | Xterra Symmetry C8 (4.6×150 mm, 3.5 μm) | 0.5                | 230           | Bulk drug                            | [92]      |
|           | Ultrapure water: Acetonitrile = 98:2, v/v | BDS Hypersil Cyano (250×4.6 mm, 5 μm) | 0.5                | 230           | Human plasma and pharmaceutical formulations | [93]      |
|           | Acetonitrile: Water = 50:50, v/v | Supelco C18 (150×4.6 mm, 5 μm) | 1.2                | λex 262       | Rat plasma                           | [94]      |
|           | | | | | | |
| **Amantadine** | Mobile phase A: Acetonitrile (5%) in water | Hypersil C18 (150×4.6 mm, 5 μm) | 1.0                | λem 430       | | |
|           | Mobile phase B: Acetonitrile Gradient programme | | | | | |
|           | Ammonium acetate buffer (0.02 M): Methanol = 12:88, v/v | Inertsil ODS-3V (250×4.6 mm, 5 μm) | 1.5                | 226           | Bulk and formulation                 | [95]      |
|           | Water: Acetonitrile = 40:60, v/v | Phenomenex RP C18 (250×4.6 mm, 5 μm) | 1.0                | 273           | Bulk and dosage formulation          | [96]      |
|           | Acetonitrile: Sodium acetate buffer (10 mmol, pH 3.5 with acetic acid): Methanol = 20:70:10, v/v/v | Nucleosil CN (250×4.6 mm, 5 μm) | 1.5                | λex 293, λem 382 | Human plasma | [97]      |
|           | Mobile phase A: 0.1% trimethylamine solution (pH 3) | Diamonsil C18 (200×4.6 mm, 5 μm) | 1.0                | 210, 280      | Quality control granules             | [98]      |
involved in the physical separation of compounds by liquid chromatography-mass spectrophotometry technique is Liquid chromatography-mass spectrophotometry. Composition phosphate buffer, pH 3.5 and methanol (80:20, v/v), product is established within 5 minute using mobile phase for UPLC are acquity BEH C8. Gradient programme: Water=99:1, v/v Acetonitrile=30:70, v/v.

Ultra pressure liquid chromatography

Ultra pressure liquid chromatography (UPLC) is obligatory in respect to the analysis time; resolution enhanced its reliability in the pharmaceutical industry. The achieved data from developed methods are robust and accurate. The common available columns for UPLC are acquty BEH C8, acquty BEH C18, acquty BEH RP18, and acquty BEH phenyl. UV-Visible detector is commonly used detector for UPLC analysis. The method for Oseltamivir and its degraded product is established within 5 minute using mobile phase composition phosphate buffer, pH 3.5 and methanol (80:20, v/v), detected at 207 nm [108].

Liquid chromatography-mass spectrophotometry

Liquid chromatography-mass spectrophotometry technique is involved in the physical separation of compounds by liquid chromatography (LC) combined mass spectrometry (MS) for mass analysis [109–113]. Liquid chromatography can be high pressure or ultra-pressure. The structure of molecule elucidate after confirming the chemical composition of charged particles with respect to mass-to-charge ratio. The molecule ionized by MS to produce fragments and its mass-to-charge ratio measured. This technique maintains high sensitivity compared to traditional techniques and selective to many applications. It has an excellent impact in the bioanalysis field mainly confronted to pharmacokinetics investigation of pharmaceuticals. Generally, LC installed octadecyl (C18) silica column but nowadays hydrophilic interaction based liquid chromatography (HILIC) has received more attention and recommended due to its potential to retain highly polar molecule with hydrophilic nature, but it needs to apply buffer as the mobile phase to minimize analyte and stationary phase ion interaction. The LCMS method that was reported for inhibitors is presented in table 2 [114–137].

Table 2: LCMS method for neuraminidase and M2 ion channel inhibitors

| Mobile phase | Stationary phase | Sample | Flow rate (ml/min) | Run time (min) | Application | Reference |
|--------------|-----------------|--------|-------------------|---------------|-------------|-----------|
| Ammonium formate (10 mmol, pH 3): Acetonitrile=20:80, v/v | Synergi C8 (150×4.6 mm, 4 µm) | Amantadine | 0.8 | 2.5 | Human plasma | [114] |
| Mobile phase A: Ammonium formate (5 mmol, in water) Mobile phase B: Acetonitrile; Gradient programme | Eclipse Plus C18 (50×3 mm, 3.5 µm) | Amantadine | --- | 5.3 | Human plasma | [115] |
| Mobile phase A: Ammonium formate (10 mmol/L, 0.1% formic acid) Mobile phase B: Acetonitrile; Gradient programme | Kinetex XB C18 (2.1×100 mm, 2.6 µm) | Amantadine, Rimantadine | 0.3 | 15 | Chicken tissue and eggs | [116] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Acetonitrile; Gradient programme | Eclipse Plus C18 (100×2.1 mm, 1.8 µm) | Zorbax SB C18 (100×2.1 mm, 3.5 µm) | 0.35 | 5 | Chicken jerky | [117] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Formic acid (0.1%) in acetonitrile; Gradient programme | ZIC-HILIC (50×2.1 mm, 5 µm) | Zanamivir | 0.4 | 15 | Milli-Q water, sewage effluent, influent and surface water | [118] |
| Acetonitrile: 0.1% Formic acid = 90:10, v/v | HydroSphere C18 (150×4.6 mm, 5 µm) | Oseletamivir and oseltamivir carboxylic acid | 0.5 | 5.5 | Human plasma | [119] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Methanol; Gradient programme | XDB C18 (2.1×150 mm, 3.5 µm) | Amantadine, Rimantadine | 0.3 | 10 | Chicken, pig, pork, duck (liver, kidney, egg) | [120] |
| Mobile phase A-Methanol: Water=1:99, v/v Mobile phase B-Methanol: Water=99:1, v/v Gradient programme | Eclipse Plus C18 (50×2.1 mm, 5 µm) | Oseletamivir and oseltamivir carboxylic acid | --- | 4.5 | Human plasma | [121] |
| Ammonium formate (10 mmol): Acetonitrile=30:70, v/v | Symmetry C18 (100×4.6 mm, 5 µm) | Oseletamivir and oseltamivir carboxylic acid | 1.0 | 2 | Human plasma | [122] |
| Ammonium acetate (10 mmol), | ZIC-HILIC (150×2.1 | Oseletamivir and oseltamivir carboxylic acid | 0.3 | 10 | Rat Plasma | [123] |
The LCMS/MS investigation revealed that low concentration of amantadine present in plasma sample, does not require any derivatization during solid phase extraction, the developed method reported successfully bioequivalence study of healthy volunteers [144]. Amantadine-d15 internal standard can be used based on protein precipitation [115]. QuEChERS extraction method applied for chicken muscle, egg pet treat sample [116, 117]. Zanamivir found in effluent sample and water from river in Japan [118]. The antiviral drugs and metabolite quantified applied flow rate (0.2–1 ml/min) having run time between 1–20 minute with biological fluids and water sample [119–129]. Ultra pressure liquid chromatography combined with the mass spectrophotometer (triple quadrupole ion

| Mobile phase | Column | Gradient programme | Elzagheid et al. | Int J Pharm Pharm Sci, Vol 11, Issue 5, 1-10 |
|--------------|--------|-------------------|-----------------|---------------------------------------------|
| Mobile phase A: Formic acid (50 mmol) in water (0.1%) | Symmetry C18 (3×150 mm, 5 μm) | 0.4 | 20 | Poultry muscle | [124] |
| Mobile phase B: Acetonitrile; Gradient programme | Mobile phase B: Methanol | 0.25 | 9 | Human plasma | [125] |
| Mobile phase A: Ammonium acetate (10 mmol, 1% acetic acid) Mobile phase B: Acetonitrile; Gradient programme | Chromatopack C18 (50×3 mm, 3.0 μm) | 0.6 | 1 | Human plasma | [127] |
| Mobile phase A: Ammonium acetate (10 mmol, 1% methanol) Mobile phase B: Acetonitrile; Gradient programme | Phenomenex Luna C8 (100×2 mm, 3 μm) | 0.2 | 3 | Human serum | [129] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Methanol; Gradient programme Mobile phase A: Ammonium acetate (10 mmol, 1% acetic acid) Mobile phase B: Acetonitrile; Gradient programme | Acquity HILIC (50×2.1 mm, 5 μm) | 0.35 | 8 | River water, sewage effluent | [132] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Methanol; Gradient programme Mobile phase A: Ammonium acetate (10 mmol), 5% acetonitrile adjusted pH 5 with acetic acid Mobile phase B: Acetonitrile; Gradient programme | BEH C18 (2.1×100 mm, 1.7 μm) | 0.7 | 8.5 | Waste and surface water | [133] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Methanol; Gradient programme Mobile phase A: Ammonium acetate (10 mmol), pH 5 with acetic acid; Gradient programme Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Methanol; Gradient programme Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Formic acid (0.1%) in methanol; Gradient programme | Acquity HSS T3 (150×2.1 mm, 1.8 μm) | 0.7 | 8.5 | River water | [134] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Methanol; Gradient programme Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Formic acid (0.1%) in methanol; Gradient programme | Acquity HSS T3 (150×2.1 mm, 1.8 μm) | 0.25 | 12 | Chicken muscle | [135] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Methanol; Gradient programme Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Formic acid (0.1%) in methanol; Gradient programme | Acquity HSS T3 (150×2.1 mm, 1.8 μm) | 0.3 | 10 | Chicken muscle | [136] |
| Mobile phase A: Formic acid (0.1%) in water Mobile phase B: Formic acid (0.1%) in methanol; Gradient programme | Acquity HSS T3 (150×2.1 mm, 1.8 μm) | 0.35 | 6 | Human plasma | [137] |

The LCMS/MS investigation revealed that low concentration of amantadine present in plasma sample, does not require any derivatization during solid phase extraction, the developed method reported successfully bioequivalence study of healthy volunteers [144]. Amantadine-d15 internal standard can be used based on protein precipitation [115]. QuEChERS extraction method applied for chicken muscle, egg pet treat sample [116, 117]. Zanamivir found in effluent sample and water from river in Japan [118]. The antiviral drugs and metabolite quantified applied flow rate (0.2–1 ml/min) having run time between 1–20 minute with biological fluids and water sample [119–129]. Ultra pressure liquid chromatography combined with the mass spectrophotometer (triple quadrupole ion...
trap) reported in feed sample illegal addition of amantadine and rimantadine [130]. Fourteen antiviral drugs detected within short time of 11 minute, multiple reaction monitoring ensured method specificity [131]. After winter season the inhibitors found in river water [132–134]. Amantadine and rimantadine are quantified in chicken muscle using different sorbent [135–136]. The UPLC method was first reported with whole blood sample, assay calculated using dried blood spot [137]. The minimum amount of sample required, elute from the column within 6 minute. The correlation coefficient of Oseltamivir and its active metabolites Oseltamivir carboxylate was greater than 0.99. Sample collection is very important parameter for this analysis. Therefore, the developed method validated successfully for human plasma of healthy volunteers.

CONCLUSION
Antiviral drugs are very useful versus influenza viruses and molecules that are actively participated for deadly diseases. The developed novel drugs are showing great potential for the prevention of influenza. It was evident that for controlling influenza, administered single dose drug to human and all animals including farm animals is required. All inhibitors can be applied during epidemic or seasonal conditions. Their main function, through vaccination, is to control the activity of viruses, reduce and manage pandemic viruses. All these mentioned drugs are also important for patients hospitalized due to influenza. Although the existing drugs are doing well, influenza experts are looking forward to identify other new drugs that exert antiviral activity like the approved ones and can be applicable as future antiviral agents for influenza viruses. Therefore, the present review gives brief information about antiviral drugs, their activity, biotransformation and analytical methods for quantification and this information will be helpful for any future studies done by experts in this field.

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AUTHORS CONTRIBUTIONS
All the author have contributed equally

CONFLICT OF INTERESTS
Both authors report no declaration of interest

REFERENCES
1. Zhu HY, Han L, Shi XL, Wang BL, Huang H, Wang X, et al. Baicalin inhibits autophagy induced by influenza virus H3N2. Antiviral Res 2011;5:62-70.
2. Fiore AE, Shlay DK, Broder K, Iskander JK, Iyeki TM, Mootrey G, et al. Centers for disease control and prevention (CDC). advisory committee on immunization practices (ACIP). Prevention and control of influenza: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomp 2008;57(RR-7):1-60.
3. Chang SC, Cheng YY, Shih SR. Avian influenza virus: the threat of a pandemic. Chang Gung Med J 2006;29:130–4.
4. Liu Y, Zhang J, Xu W. Recent progress in rational drug design of neuraminidase inhibitors. Curr Med Chem 2007;14:2972–91.
5. Zhang Z. Spatio-temporal data comparisons for global highly pathogenic avian influenza (HPAI) H5N1 outbreaks. PLoS One 2010;5:e15314.
6. Tanaka T. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. Can Med Assoc J 2009;181:155–8.
7. Laver WG, Bischofberger N, Webster RG. Disarming flu viruses. Sci Am 1999;280:78–97.
8. Laver WG, Bischofberger N, Webster RG. The origin and control of pandemic influenza. Perspect Biol Med 2000;43:173–92.
9. Palese P, Schulman JL, Bodo G, Meindl P. Inhibition of influenza and parainfluenza virus replication in tissue culture by 2-deoxy-2,3-dehydro-N-trifluoro-acetylnearminic acid (FANA). Virology 1974;59:490–8.
10. Russell RJ. The structure of H5N1 avian influenza neuraminidase suggests new opportunities for drug design. Nature 2006;443:45–9.
11. Pinto LH, Holsinger IJ, Lamb RA. Influenza virus M2 protein has ion channel activity. Cell 1992;69:17–27.
12. Hayden FG. Amantadine and ribavirin-clinical aspects. In: Richman DD. editor. Antiviral Drug Resistance. New York: John Wiley and Sons, Inc; 1996. p. 59–77.
13. Hay AJ, Wolstenholme AJ, Skehel JJ. The molecular basis of the specific anti-influenza action of amantadine. The EMBO J 1985;4:3021–4.
14. Sidwell RW, Huffman JH, Barnard DL. Inhibition of influenza virus infections in mice by GS4104, an orally effective influenza virus neuraminidase inhibitor. Antiviral Res 1998;37:107–20.
15. Monto AS, Fleming DM, Henry D. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. J Infect Dis 1999;180:254–61.
16. Monto AS. The role of antivirals in the control of influenza. Vaccine 2003;21:1796–800.
17. McKimm BJ. Management of influenza virus infections with neuraminidase inhibitors: detection, incidence, and implications of drug resistance. Treat Respir Med 2005;4:107–16.
18. Wade RC. Flu and structure-based drug design. Structure 1997;5:1139–45.
19. Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. Lancet 2000;355:827–35.
20. Laver WG. From the great barrier reef to a “Cure” for the flu: tall tales, but true. Perspect Biol Med 2004;47:590–6.
21. Muthuri SC. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1 pdm09 virus infection: a meta-analysis of individual participant data. Lancet Resp Med 2014;2:395–404.
22. Heneoglan QJ. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess 2016;20:1–242.
23. Luo M. Structural biology: antiviral drugs fit for a purpose. Nature 2006;443:37–38.
24. McLaughlin MM, Skoglund EW, Ison MG. Peramivir: an intravenous neuraminidase inhibitor. Expert Opin Pharmacother 2015;16:1889–900.
25. Yamashita M. CS-8958, a prodrug of the new neuraminidase inhibitor R-125489, shows long-acting anti-influenza virus activity. Antimicrob Agents Chemother 2009;53:186–92.
26. Burger RA. Immunological effects of the orally administered neuraminidase inhibitor oseltamivir in influenza virus-infected and uninfected mice. Immun Pharma 2000;47:45–52.
27. Klumpp K, Graves BJ. Optimization of small molecule drugs binding to highly polar target sites: lessons from the discovery and development of neuraminidase inhibitors.Curr Top Med Chem 2006;6:423–34.
28. Vavricka CJ. Structural and functional analysis of laninamivir and its octanoate prodrug reveals group specific mechanisms for influenza NA inhibition. PLoS Pathog 2011;7:e1002249.
29. Bright RA, Medina MJ, Xu X, Perez Oronoz G, Wallis TR. Incidence of adamantine resistance among influenza A [H3N2] viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005;366:1175–81.
30. Bright RA, Shlay DK, Shu B, Cox NJ, Klimov A. Adamantane resistance among influenza viruses isolated early during the 2005–2006 influenza season in the United States. JAMA: J Am Med Assoc 2006;295:891–4.
31. Duque MD, Valderve E, Barniol M, Guardiola S, Roy M. Inhibitors of the M2 channel of influenza virus. Recent Adv Pharm Sci 2011;2:35–64.
32. Govorkova EA, McCullers JA. Therapeutics against influenza. Curr Top Microbiol Immunol 2013;370:273–300.
33. Heneus A. Unpacking the incoming influenza virus. Cell 1992;69:577–80.
34. Wattanagoon Y, Stepniewska K, Lindegarth N. Pharmacokinetics of high-dose oseltamivir in healthy volunteers. Antimicrob Agents Chemother 2009;53:945–52.
35. Dukowski R, Smith JR, Davies RE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents 2010;35:461–7.
36. Sharma PP, Roy RK, Anurag. Neuraminidase inhibitors: Oseltamivir, Peramivir; synthesis and profile. J Pharm Res 2010;3:1602-6.

37. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 6-0802. Clin Pharmacokinet 1999;36(Suppl 1):S33-S38.

38. Doucette KE, Aoki FY. Oseltamivir: a clinical and pharmacological perspective. Expert Opin Pharmacother 2001;2:1671-83.

39. Glaxo Smith Kline. Safety study to assess IV zanamivir for treatment of influenza infection in patients who are in hospital. [Available from: http://clinicaltrials.gov/ct2/show/NCT01014988. [Last accessed on 11 Feb 2011]]

40. Glaxo Smith Kline. A study of intravenous zanamivir versus oral oseltamivir in adults and adolescents hospitalized with influenza (ZORO). Available from: http://clinicaltrials.gov/ct2/show/NCT01013620. [Last accessed on 11 Feb 2011]

41. Cass LM, Brown J, Pickford M. Pharmacoscientific evaluation of lung deposition of inhaled zanamivir in healthy volunteers. Clin Pharmacokinet 1999;36(Suppl 1):21-31.

42. Bergstrom M, Cass LM, Valind S. Deposition and disposition of [11C] zanamivir following administration as an intranasal spray: evaluation with positron emission tomography. Clin Pharmacokinet 1999;36(Suppl 1):S33-S38.

43. Peng AW, Milleri S, Stein DS. Direct measurement of the antiinfluenza agent zanamivir in the respiratory tract following inhalation. Antimicrob Agents Chemother 2009;44:1974-6.

44. Caffee DP, Peng AW, Cass LM, Lobo M, Hayden FG. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza a virus infection. Antimicrob Agents Chemother 1999;43:16:16-20.

45. Bantia S, Parker CD, Ananth SL, et al. Comparison of the antiinfluenza virus activity of RMW-27001 with those of oseltamivir and zanamivir. Antimicrob Agents Chemother 2001;45:1165-7.

46. Kohno S, Kida H, Mizuguchi M, Shimada J. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. Antimicrob Agents Chemother 2010;54:4568-74.

47. Itch Y, Shinya K, Kiso M. In vitro and in vivo characterization of a new swine-origin H1N1 influenza viruses. Nature 2009;460:1021-5.

48. Yamashita M, Tomozawa T, Kukuta M, Tomozawa A, Nasu H, Kubo S. CS-8958, a prodrug of the new neuraminidase inhibitor, in human pulmonary tissue. Drug Absorption, distribution and excretion of amantadine by the elderly. Eur J Clin Pharm 1975;8:349-51.

49. Montanari C, Ferrari P, Bavazzano A. Urinary excretion of amantadine in patients with chronic liver disease. Clin Pharmacol Ther 1987;42:249-54.

50. Rubin FR, Fukuda EK, Garland WA. Urinary metabolites of rimantidine in humans. Drug Metab Dispos 1988;16:773-7.

51. Wills RJ. Update on rimantidine’s clinical pharmacokinetics. J Respir Dis 1999;20(Suppl 3):S29-S50.

52. Rubin FA, Choma N, Fukuda EK. Determination of rimantidine and its hydroxylated metabolites in human plasma and urine. J Chromatogr 1989;497:147-57.

53. Brown SY, Garland WA, Fukuda EK. Isolation and characterization of an unusual glucuronide conjugate of rimantidine. Drug Metab Dispos 1990;18:546-7.

54. Youssif RM, El-Yazbi EA, Khamis EF, Younis SE. Validated spectrophotometric methods for the evaluation of oseltamivir counterfeited pharmaceutical capsules; Bull Fac Pharm Cairo Uni 2014;5:263-9.

55. Bano T, Yadav G, Dudhe R. Development and validation of oseltamivir phosphate API by UV-spectrophotometer. Global J Pharm 2013;7:294-7.

56. Raut CS, Gharde DS, Dhahale PN, Gondari JD, Hosmani AH, Hosmani AH. Development and validation of oseltamivir phosphate in flour by UV-spectrophotometer. Int J PharmTech Res 2010;2:363-5.

57. Kumar JVS, Prasanthi S, Guruvaiah M, Sekaran CB. Application of potassium permanganate to the spectrophotometric determination of oseltamivir phosphate in bulk and capsules. Asian J Pharm Clin Res 2012;5:18-22.

58. Nebens M, Fattah SAA, Hassan DW, Youssif NF. Spectrophotometric and spectrofluorimetric determination of oseltamivir phosphate using 4-chloro-7-nitrobenzo-2-oxa-1, 3-diazole. Anal Chem Indian J 2011;10:336-41.

59. Mahmoud AM, Khalil NY, Darwich IA, Aboul-Fadl T. Selective spectrophotometric and spectrofluorimetric methods for the determination of amantadine hydrochloride in capsules and plasma via derivatization with 1, 2-naphthoquinone-4-sulfonate. Int J Anal Chem 2009;81:010:4. Doi: 10.1155/2009/810104.

60. Gursoy A, Ozkirimli S, Erosoy O. Spectrophotometric determination of amantadine hydrochloride in capsules. J Fac Pharm Istanbul 1998;32:63-8.

61. Choi K, Choi JK, Yoo GS. Spectrophotometric determination of amantadine sulfate after ion-pairing with methyl orange. Arch Pharm Res 1991;14:285-9.

62. Musalska I, Sobczak A, Kiaszwicz I, Rabiega K, Lesniewska MA, Jelinska A. 1, 2-Naphthoquinone-4-sulfonic acid sodium salt as a reagent for spectrophotometric determination of rimantidine and memantine. Int J Anal Chem 2015;2015:320-7.

63. Bano T, Dudhe R, Kumar N. Development and validation of rp-hplc method for the determination of oseltamivir phosphate API. J Progr Res Chem 2015;2:69-73.

64. Kumar NM, Abbulu K, Narayana BV. Development and validation of stability indicating rp-hplc method for the determination of oseltamivir phosphate in oseltamivir phosphate capsules. Int J Res Environ 2015;5:544-53.

65. Junaidy MAQ, Haque MA, Bakshi V. Rp-hplc method development and validation for the estimation of oseltamivir phosphate in bulk form and pharmaceutical formulations. Int J Pharm Pharm Sci 2012;4:2768-61.

66. Ameti A, Slavkovska J, Starkoska K, Sarafinovska ZA. A simple isocratic rp-hplc method for quality control of oseltamivir capsules. Maced J Chem Eng 2012;3:205-15.

67. Sharma YK, Agrawal DW, Bhure S, Rathore SS, Rawat C, Mukharjee R. Synthesis, characterization and determination of process-related impurities in oseltamivir phosphate. E-J Chem 2012;9:113-20.
80. Malpatil SM, Jahan K, Pritil SK. Development and validation of rp-hplc method for the determination of oseltamivir phosphate in bulk drug and in dosage. Indo-Global J Pharm Sci 2011;1:57–62.

81. Sharma MC, Sharma S. Dissolution assessment and hplc method development and validation of oseltamivir phosphate in pharmaceutical formulation. Int J Basic Appl Sci 2011;3:325–8.

82. Zeynep A, Sena C, Sidika T. Rp-hplc method for determination of oseltamivir phosphate in capsules and spiked plasma. Anal Lett 2010;43:2200–9.

83. Nagarajan JSK, Muraldihran S. A validated rp-hplc method for estimation of Oseltamivir in pharmaceutical formulation. Der Pharm Lett 2009;1:162–8.

84. Green MD, Nettey H, Wirtz RA. Determination of oseltamivir quality by colorimetric and liquid chromatographic methods. Emer Infect Dis 2008;14:552–6.

85. Narasimhan B, Abida K, Srinivas K. Stability indicating rp-hplc method development and validation for oseltamivir apl. Chem Pharm Bull 2009;56:413–7.

86. Raghumur P, Raju IVS, Reddy R, Srimulu J. A stability indicating lc method for oseltamivir phosphate. Anal Chem Indian J 2008;6:137–24.

87. Bahrami G, Mohammadi B, Kiani A. Determination of oseltamivir carboxylate in human serum by solid phase extraction and high performance liquid chromatography with uv detection. J Chromatogr B 2008;864:38–42.

88. Charles JJ, Geneste C, Kummer EL, Gheyrouche R, Boudis H, Dubost JP. Development and validation of a rapid hplc method for the determination of oseltamivir phosphate in Tamiflu and generic versions. J Pharm Biomed Anal 2007;44:1008–13.

89. Rajendran R, Devika S, Sura RS, Sunil V, Kumar MB, Gopinath P, et al. Rp-hplc pd method for estimation of zanamivir in api and pharmaceutical formulation. Ind Am J Pharm Sci 2018;5:2110–6.

90. Bhirud CH, Nandal DH. Stability indicating rp-hplc and hptlc methods for the determination of zanamivir in bulk and dosage form. Int J Pharm Sci 2016;8:249–56.

91. Reddy YR, Harika KSL, Sowjanya KS, Swathi E, Sowjanya B, Reddy SS. Estimation of zanamivir drug present in tablets using rp-hplc method. Int J PharmTech Res 2011;3:180–6.

92. Bhoopyawat B, Srinawi N, Ma Y, Steventon GB. A validated HPLC method for zanamivir and its application to in vitro permeability study in cao-2 culture model. Indian J Pharm Sci 2011;73:564–8.

93. Fok N. A validated HPLC method for the determination of the neuraminidase inhibitor, zanamivir (gg67) in spiked human plasma and in pharmaceutical formulations. J Liq Chromatogr Related Technol 2004;27:1541–52.

94. Wang F, Zhang S, Sheng C, Zhao X, You J. Sensitive determination of amantadine in microdialysis samples from rat plasma by HPLC with fluorescence detection. J Liq Chromatogr Relat Technol 2013;35:2012–8.

95. Yanamadala G, Lavanya N, Srikumar PP. A pre-column derivatization technique for the development and validation of a HPLC-UV method for the determination of amantadine hydrochloride in bulk and formulations by using (2-naphthyl) acetyl chloride. Acta Chim Pharm Indica 2014;4:170–9.

96. Vemuri SK, Krishna NR, Mohammad MJ, Nalluri BN. Analysis of amantadine hydrochloride-phenyl isothiocyanate complex in bulk and pharmaceutical dosage forms by rp hplc-pda method. Br J Pharm Res 2014;4:278–88.

97. Darwish IA, Aboul FT, Kahlil NY, Mahmoud AM, Al-Obaid AM. Sensitive new hplc method for evaluation of the pharmacokinetics of new amantadine prodrugs as hepatic delivery systems to enhance its activity against HCV. Int J Res Pharm Sci 2010;1:151–7.

98. Yihua Z, Jinguo J, Xuejing H, ShiLang Z. Simultaneous determination of three components in pediatric paracetamol and amantadine hydrochloride granules using high performance liquid chromatography with gradient elution and dual wavelength detection. Chin J Chromatogr 2010;28:1005–8.

99. Shuangjin C, Fang F, Han L, Ming M. New method for high-performance liquid chromatographic determination of amantadine and its analogues in rat plasma. J Pharma Biomed Anal 2007;44:1100–5.

100. Higashi Y, Uemori I, Fujiy Y. Simultaneous determination of amantadine and rimantadine by hplc in rat plasma with pre-column derivatization and fluorescence detection for pharmacokinetic studies. Biomed Chromatogr 2005;19:665–62.

101. Mamatha J, Devanna N. Development and validation of a rp-hplc method for the analysis of rimantadine hydrochloride in medicinal form. Rasayan J Chem 2018;11:300–6.

102. zacharis CK, Tzanavaras PD, Vlisiddis AG. Determination of rimantadine in human urine by hplc using a monolithic stationary phase and on-line post-column derivatization. J Sep Sci 2013;36:901–6.

103. Bhirud CH, Nandal DH. Development and validation of stability indicating hplc method for the determination of oseltamivir phosphate in bulk and dosage form. Int J Pharm Res Pharma 2017;9:299–311.

104. Al Bratty M, Saleh SF, Alhazmi HA, Javed SA, Ahmed AM, Ahsan W. A validated hptlc densitometric method for quantitative determination of zanamivir in bulk and pharmaceutical formuation. Eur J Chem 2018;9:115–20.

105. Kummer EL, Gaudin K, Charles JJ, Gheyrouche R, Boudis H, Dubost JP. Development and validation of a rapid capillary electrophoresis method for the determination of oseltamivir phosphate in Tamiflu and generic versions. J Pharm Biomed Anal 2009;50:544–6.

106. Pazourek J, Revilla AL, Gajdosova D, Havel J. Validation of a capillary zone electrophoresis method for determination of rimantadine hydrochloride in rimantadine 100 tablets and the method application to dissolution test monitoring. Drug Dev Ind Pharm 2016;42:125–34.

107. Revilla AL, Hamacek J, Lubal P, Havel J. Determination of rimantadine in pharmaceutical preparations by capillary zone electrophoresis with indirect detection or after derivatization. Chromatogr 1998;47:433–9.

108. Rashed NS, Abdallah OM, Said NS. Validated stability-indicating methods for determination of oseltamivir phosphate. Br J Pharm Res 2017;16:1-9.

109. Mehta SD, Pailwal S. Phytochemical analysis, liquid chromatography, and mass spectroscopy and in vitro anticaner activity of annona squamosa seeds linn. Asian J Pharm Clin Res 2018;11:101–3.

110. Nagappan K, Yamjala K, Sathyaseelan M, Byran G. Stability evaluation of tartrazine by liquid chromatography-diode array detector and high-resolution electron spray ionization quadrupole time-of-flight mass spectrometry/mass spectrometry analysis. Asian J Pharm Clin Res 2017;10:295–9.

111. Pirani V, Sojita R, Raj H, Jain V. Chromatographic method for ibesartan and its combination with other drug. J Crit Rev 2015;2:7-11.

112. Pradeep PS, Shrungesh KTO, Prashantha N, Mahadevan KM. Synthesis, in vitro antibacterial, toxicity and molecular docking anticancer activity of novel n-[2-choroquinolin-3-y] methyldiene]-2-aniline Schiff bases. Int J Curr Pharm Res 2015;7:37–46.

113. Yahdiana H, Norma A, Harmita. Method development and validation of leucanidic acid in human plasma by liquid chromatography tandem-mass spectrometry. Int J Appl Pharm 2018;10:87-91.

114. Bhadoriya A, Rathnam S, Dasandi B, Parmar D, Sanyal M, Shrivastav PS. Sensitive and rapid determination of amantadine without derivatization in human plasma by LC-MS/MS for a bioequivalence study. J Pharm Anal 2018;8:202−7.

115. Wang K, Chen M, Weng H, Gao Y, Zhao H, Lin Z. Validation of a robust and high-throughput hplc-ms/ms method to determine Amantadine levels in human plasma. J Bioanal Biochem 2018;4:51-61.

116. Tsurowka Y, Nakajima T, Kanda M, Hayashi H, Matsuhashita Y, Yoshikawa S, et al. Simultaneous determination of amantadine, rimantadine, and memantine in processed products, chicken tissues, and eggs by liquid chromatography with tandem mass spectrometry. J Chromatogr B 2017;1044–1045:142–8.

117. Turnipseed SB, Storey JM, Andersen WC, Filigenzi MS, Heise AS, Larson SK. Development and validation of a robust and high-throughput hplc-ms/ms method for determination of amantadine and its analogues in chicken jerky pet treats. J Agric Food Chem 2011;59:6968–78.
118. Lindberg RH, Fedorova G, Blum RM, Pulit-Prociak J, Gilman A, Jarhult J, et al. Online solid phase extraction liquid chromatography using bonded awitentronic stationary phases and tandem mass spectrometry for rapid environmental trace analysis of highly polar hydrophilic compounds—application for the antiviral drug oseltamivir. J Chromatogr B 2012;891–892:57–63.

119. Janiwarad S, Haq KJ, Choudhary D. A selective and sensitive liquid chromatographic/tandem mass spectrometric method for simultaneous estimation of oseltamivir and its metabolite oseltamivir carboxylic acid in human plasma for bioavailability or bioequivalence studies. World J Pharma Res 2014;3:4598–614.

120. Zhao S, Li D, Qiu J, Wang M, Yang S, Chen D. Simultaneous determination of amantadine, rimantadine and chlorpheniramine in animal derived food by liquid chromatography-tandem mass spectrometry after fast sample preparation. Anal Methods 2014;6:7062–7.

121. Hu ZY, Laizure SC, Meibohm B, Herrington WL, Parker RB. Simple and sensitive assay for quantification of oseltamivir and its active metabolite oseltamivir carboxylate in human plasma using high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry: improved applicability to pharmacokinetic study. J Pharma Biomed Anal 2013;72:245–50.

122. Gupta A, Guttikar S, Shrivastav PS, Sanyal M. Simultaneous quantification of prodrug oseltamivir and its metabolite oseltamivir carboxylate in human plasma by LC-MS/MS to support a bioequivalence study. J Pharma Anal 2013;3:149–60.

123. Lin CC, Yen JC, Wu YT, Lin LC, Tsai TH. Chemical analysis and transplacental transfer of oseltamivir and oseltamivir carboxylic acid in pregnant rats. PLoS One 2013;7:e46062.

124. Berendsen BJA, Weghs RS, Essers ML, Stolker AAM, Weigel S. Quantitative trace analysis of a broad range of antiviral drugs in poultry muscle using column-switch liquid chromatography coupled to tandem mass spectrometry. Anal Bioanal Chem 2012;402:1611–23.

125. Kromdijk W, Rosing H, Van den Broek MPH, Beijnen JH, Huijtema ADR. Quantitative determination of oseltamivir and oseltamivir carboxylate in human fluoride EDTA plasma including the ex vivo stability using high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry. J Chromatogr B 2012;891–892:57–63.

126. Lindegardh N, Hanpithakpong W, Kamanikom B, Farrar J, Hien TT, Singhhasivanon P, et al. Quantification of the anti-influenza drug zanamivir in plasma using high-throughput HILIC-MS/MS. Bioanal 2011;3:157–65.

127. Kanneti R, Bhaves D, Paramar D, Shrivapaksh R, Bhatt PA. Development and validation of a high-throughput and robust LC-MS/MS with electrospray ionization method for simultaneous quantitation of oseltamivir phosphate and its oseltamivir carboxylate metabolite in human plasma for pharmacokinetic studies. Anal Bioanal Chem 2011;403:1611–23.

128. Baughman TM, Wright WL, Hutton KA. Determination of zanamivir in rat and monkey plasma by positive ion hydrophilic interaction chromatography (HILIC)/tandem mass spectrometry. J Chromatogr B 2007;852:505–11.

129. Arndt T, Gueggenren B, Holh A, Reis J. Determination of serum amantadine by liquid chromatography-tandem mass spectrometry. Clin Chim Acta 2005;359:125–31.

130. Jia Q, Li D, Wang X, Yang S, Qian Y, Jia J. Simultaneous determination of amantadine and rimantadine in feed by liquid chromatography-Qtrap mass spectrometry with information-dependent acquisition. Anal Bioanal Chem 2018;410:5555–65.

131. Mu P, Xu N, Chai T, Jia Q, Yin Z, Yang S, et al. Simultaneous determination of 14 antiviral drugs and relevant metabolites in chicken muscle by UPLC-MS/MS after QuEChERS preparation. J Chromatogr B 2016;1023–1024:17–23.

132. Azuma T, Ishiuchi H, Inoyama T, Teranishi Y, Yamaoka M, Sato T, et al. Detection of peramivir and laninamivir, new anti-influenza drugs, in sewage effluent and river waters in Japan. PLoS One 2015;10:e0131412.

133. Takami R, Ozaki H, Giri RR, Taniguchi S, Hayashi S. Antiviral drugs zanamivir and oseltamivir found in wastewater and surface water in Osaka, Japan. J Water Environ Tech 2012;10:57–68.

134. Takami R, Ozaki H, Giri RR, Taniguchi S, Hayashi S. Detection of antiviral drugs oseltamivir phosphate and oseltamivir carboxylate in neya river, Osaka, Japan. J Water Environ Tech 2010;8:363–72.

135. Yan H, Liu X, Cui F, Yun H, Li L, Ding S, et al. Determination of amantadine and rimantadine in chicken muscle by QuEChERS pretreatment method and UHPLC coupled with LTQ Orbitrap mass spectrometry. J Chromatogr B 2013;938:8–13.

136. Wu YL, Chen RX, Yue X, Yang T, Zhao J, Zhu Y. Simultaneous determination of amantadine, rimantadine and memantine in chicken muscle using multi-walled carbon nanotubes as a reversed-dispersive solid phase extraction sorbent. J Chromatogr B 2014;965:197–205.

137. Hooff GP, Meesters RJW, Van Kampen JJA, Van Huizen NA, Koch B, Al Hadithy AFY, et al. Dried blood spot UHPLC-MS/MS analysis of oseltamivir and oseltamivir carboxylate—a validated assay for the clinic. Anal Bioanal Chem 2011;400:3473–79.