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Introducing Aprepitant ingested Ultrafast dissolving film for the treatment of Emetogenic Chemotherapy

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ABSTRACT:
Aprepitant loaded nano fibres was prepared using Electrostatic spinning (Electrospinning, ES), as a potential orally dissolving dosage form. Different polymers were performed in order to fabricate a consistent and removable web on the collector with ultra-fast dissolution in water based media. The most appropriate for this purpose is poly vinyl-alcohol because of its low molecular weight. Using Scanning electron microscope [SEM] morphology of the prepared nano-fibres was characterized and also functions of viscosity and drug content was showed. With narrow distribution, the diameters of the fibres were between 100 and 300 nm. In vitro drug release of the webs was immediate (less than 30s) after immersion independently of their drug content owing to the formed huge surface area, while cast films with the same compositions and commercial tablets needed 30 min or more for complete dissolution. The developed technology for the preparation of orally dissolving nano-fibre (ODW) formulations is a promising way for producing effective and acceptable dosage forms for children, older people and patients with chemotherapy induced nausea and vomiting.

Keywords: Electrospinning, Scanning electron microscope, particle size distribution, In vitro drug release.

INTRODUCTION

Aprepitant is a medication used to manage and treat chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). It is in the neurokinin-1 antagonist class of medications. This activity outlines and reviews the indications, actions, and contraindications for aprepitant as a valuable agent in preventing and managing CINV and PONV. This activity will also highlight the mechanism of action, adverse event profile, and other key factors (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions) pertinent for members of the healthcare team in the management of patients either receiving highly emetogenic chemotherapy or general anesthesia.

Nausea is the subjective experience of an unpleasant, wavelike sensation in the back of the throat and/or the epigastrium that may culminate in vomiting (emesis). Vomiting (emesis) is the forceful expulsion of the contents of the stomach, duodenum, or jejunum through the oral cavity. Retching involves the gastric and esophageal movements of vomiting without expulsion of vomit; it is also referred to as dry heaves.

Progress has been made in understanding the neuro-physiological mechanisms that control nausea and vomiting (N&V). Both are controlled or mediated by the central nervous system but by different mechanisms. Nausea is mediated through the autonomic nervous system.

Neurotransmitters (including serotonin, substance P, and dopamine) found in the CTZ, the vomiting centre (thought to be located in the nucleus tractus solitarius), and enterochromaffin cells in the gastrointestinal tract release efferent impulses. These impulses are transmitted to the abdominal musculature, salivation centre, and respiratory centre. The relative contribution from these multiple pathways, culminating in N&V symptoms, is complex. It is postulated to account for agents' variable emetogenicity (intrinsic emetogenicity and mitigating factors [i.e., dosage, administration route, and exposure duration]) and emetogenic profile (i.e., time to onset, symptom severity, and duration).

The electrospinning process is highly versatile and allows not only the processing of many different polymers into polymeric nano-fibres but also the co-processing of polymer mixtures and mixtures of polymers and low-molecular-weight nonvolatile materials. This is done simply by using ternary solutions of the components for electrospinning to form a

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combination of nano-fibre functionalities. Polymer blends, core–shell structures, and side-by-side bi-component electrospinning are growing research areas that are connected with the electrospinning of multi-component systems. The targets are either to create nano-fibres of an "un-spinnable" material or to adjust the fibre morphology and characteristics.

MATERIALS AND METHODS[3-17]

DRUG: Aprepitant was purchased from Sai Mirra Iino Pharm, India and all other reagents used were of highest purity and analytical grade. Double distilled water was used throughout the experimental work.

PREFORMULATION STUDIES[3-9]

Analytical validation of drug

To validate the drug and construct the calibration curve, UV visible spectrophotometric technique is employed.

Drug – excipient compatibility

The drug-excipient compatibility studies are carried out with an intent to identify, quantify and predict potential interactions (physical or chemical) along with the impact of these interactions on the manufacturability, quality and performance of the final drug product.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

FTIR study is carried out to check the compatibility of drug with polymers. Infrared spectrum of oxcarbazepine is determined on Fourier transform Infrared spectrophotometer using KBr dispersion method. The baseline correlation is done using dried potassium bromide. Then the spectrum of dried mixture of drug and Pottasium bromide is run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

FORMULATION OF AED CONTAINING NANOFIBRE[10-19]

Nanofibre is formulated by:

a. By electrospinning method
b. By solvent casting method

Electrospinning method

In the electrospinning process, the initial electrospinning fluid gradually changes its morphology after the voltage is applied, until it reaches the critical voltage shape into a Taylor cone. When the liquid jet stretches over a certain distance, it enters the bending and whiplash stage. With the solvent volatilization, the jet is stretched to micrometers or even tens of nano meters, finally solidified and deposited on the collector to form nano fibre. On the basis of this principle, the electrospinning process can be adjusted by system parameters (polymer type, molecular weight, viscosity, conductivity of the solution, surface tension), process parameters (voltage, flow rate, receiving distance) and environmental parameters (humidity, temperature) to change the morphology and size of nano fibres. As a simple, top-down one-step preparation method, electrospinning technology produces nano fibres with small pore size, high porosity and a structure similar to ECM. Therefore, it has received extensive attention from researchers and used to prepare functionalized nano fibres for applications in biomedicine and other fields. At the same time, the electrospinning technology is continuously upgraded and optimized.

Solvent casting method

Polymer solution casting is a technique that can replace film extrusion to deliver high-quality films with superior optical, mechanical and physical film properties. In polymer solution casting, polymer is dissolved or dispersed in solution, coated onto a carrier substrate, and then the water or solvent is removed by drying to create a solid layer on the carrier. The resulting cast layer can be stripped from the carrier substrate to produce a standalone film. Before or after stripping, the cast film can be laminated with other webs or coated with other materials to create multi-layer products.

EVALUATION OF AED CONTAINING NANOFIBRE[20-27]

Particle size & zeta potential analysis

Particle size analysis is used to characterize the size distribution of particles in the formulation. Zeta Potential is the characterization of the electrokinetic potential of liquid-liquid or solid-liquid colloidal dispersions. It is carried out using Malvern Zetasizer.

Entrapment efficiency

Entrapment efficiency of nano carriers can be calculated by using the indirect method, the un-

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entrapped or free amount is estimated in the supernatant after centrifugation.

Drug content determination

Determination of the drug content of the preparations, sample solutions prepared by the dissolution of the dosage forms have to be analysed using calibration graphs of high slope in narrow concentration ranges.

XRD studies

X-Ray Diffraction, frequently abbreviated as XRD, is a non-destructive test method used to analyze the structure of crystalline materials. XRD analysis, by way of the study of the crystal structure, is used to identify the crystalline phases present in a material and thereby reveal chemical composition information.

X-ray diffraction (XRD) obtained for targeted ODF sample using X-ray diffractometer (D8 Phaser, Bruker AXS GmbH, Germany). The X-ray generator was operated at 30 kV and 10 mA employing Co tube at λ 1.79026 Å as a radiation source and using LYNXEYE detector. The angular range (2θ) varied from 4 to 50° at a scanning rate of 0.02° 2θ s−1 and measured at 0.24s/step. The diffraction patterns were produced as counts per step which were analysed using Topas software (Bruker, AXS).

In vitro drug release

The In vitro release study is a critical test to assess the safety, efficacy, and quality of nano-particle-based drug delivery systems, but there is no compendial or regulatory standard. The variety of testing methods makes direct comparison among different systems difficult.

900 ml of o.1 N HCL is used as a media, at is maintained at 37 +0.5 °c while the basket is set at 100 rpm. A film sample of 4 cm2 (2×2 cm) is cut and taken into the basket. 5 ml of the sample were taken every 2 minutes and the same amount is replaced with fresh 0.1 N HCL. The withdrawn samples were filtered and analyzed using a UV spectrometer at a wavelength of 267 nm. In-vitro dissolution profile data of all formulations is given. The Percentage Cumulative Drug Release of F1 - F9. The in-vitro dissolution profile data of marketed formulation depicted. The comparison of in-vitro release data of marketed formulation.

SEM Analysis

The morphology of the nanofibres is to be investigated with a scanning electron microscope (SEM). The samples are fixed by a double-sided carbon adhesive tape and then coated by a sputtered gold conductive layer. Performing a visual analysis of a surface using scanning electron microscopy contributes to the identification of contaminates or unknown particles, the cause of failure and interactions between materials.

SEM images were obtained using a JSM-IT300 (Manufacture JEOL, JAPAN). A 2x2 mm piece of the film was mounted on a double adhesive carbon tape placed on an aluminium tub. Samples were analysed at low vacuum without further coating.

FORMULATION OF NANOFIBRE LOADED ULTRAFAST DISSOLVING OROFILM[28-29]

The formulated nano-fibre is loaded into ultrafast dissolving orofilm by solvent evaporation technique.

EVALUATION OF ULTRAFAST DISSOLVING OROFILM[30-34]

Physical evaluation

Properties such as homogeneity, colour, transparency and surface of LMN ODFs are inspected visually.

Thickness Measurements

The thickness of the films is essential to be uniform as it is directly associated to the precision of the dose. Films are evaluated for thickness by using micrometer screw gauge.

Surface pH study

The surface pH of the oro-dispersible film is calculated in order to investigate the possibility of any side effects in vivo, as acidic or alkaline pH may cause irritation or inflammation to the oral mucosa and it is measured to maintain the surface pH as close to neutral as possible. The film is placed in a petri dish and slightly moistened with the help of 1 ml of distilled water and kept for 30 seconds; pH is measured by bringing the electrode in contact with the surface of the film and allowing it to stand for 1 minute. This study is performed three times for each film and the mean ± S.D is calculated.

Weight variation

Three films of 2 × 2 cm2 size were cut randomly from each film formulation. Films were weighed individually on electronic balance and the mean weight for each batch was calculated [15].

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Preparation of artificial saliva

The artificial saliva solution was prepared in various method. To prepare a litre of artificial saliva 2.382 g of disodium hydrogen phosphate was dissolved in 500 ml distilled water. Then 0.190 g of potassium dihydrogen phosphate (0.019%) and 8 g of sodium chloride (0.8%) were added to form a homogenous saliva solution. The final volume was adjusted to 1 L using distilled water. The pH of the solution was further adjusted to 6.75 with phosphoric acid and was used as test medium for disintegration.

Drug content uniformity

Films are placed in100ml volumetric flask and dissolved in simulated saliva pH 6.8 solutions. The contents are stirred with magnetic stirrer to dissolve the films and the volume is completed then filtered through Whatmann filter paper no. 41, to separate out the insoluble excipient. The absorbance of the solution is measured at 267nm against the corresponding blank (UV visible spectrophotometer UV- 1601 Shimadzu Corporation, Japan).In case of HPMC films, distilled water is used to dissolve the film and then suitably diluted with artificial saliva (pH 6.8). The estimations are carried out in triplicate.

Disintegration time

The 180 s limit identified by European Pharmacopeia was employed with a set target of 60 s. The film was placed in a beaker containing 10 ml of artificial salvia (pH 6.75). To simulate in vivo conditions the test was performed in 10 ml of artificial saliva. The ODF was placed horizontally in a 30 ml beaker with 10 ml of artificial salvia media. Beaker was placed in a larger beaker containing 100 ml distilled water, and the temperature was maintained at 37 °C using hot plate. Magnetic stirrer was used set at 10 rpm. All studies were performed in triplicate for each formulation. The disintegration time was determined when the film dissolved or fragmented into small pieces.

Folding endurance

The folding endurance is expressed as the number of folds required for breaking the specimen or developing visible cracks. This gives an indication of brittleness of the film.

Films of 2×3cm2 were subjected to this test by folding the film at the same point repeatedly.

Film quality

The quality of the produced films was assessed based on 5 criteria. Each criterion was given 20% of the total value. The criteria include 1) film flexibility (endurance >30 times), 2) good spreadability upon pouring onto the casting tray, 3) not sticky film, 4) easy to peel off casting tray, and 5) smooth appearance.

Mechanical properties

The mechanical properties of the ODFs were evaluated using Instron universal testing machine (Instron, USA), with load cell 50 N. Films with size 3x2 cm2 were attached on two clamps at the distance at 30 mm. These films were pulled by two clamps at rate of 50 mm/min. The parameters of mechanical properties including tensile strength and % elongation were assessed. Three samples per batch were used and results are reported as mean ± SD. Tensile strength was measured using the Eq.

Tensile strength (MPa) = (Load at failure Film thickness × film width) × 100

Whereas % elongation was determined by the following equation:

Percentage Elongation (%) = Change in Length Initial Length ×100

Author conclusion

The Author concluded that the aim of research work was to formulate FDFs by employing the 32 central composite design and evaluate different for mutations of fast dissolving films of anti-emetic drug aprepitant to achieve faster drug release to control in nausea and vomiting. In vivo studies showed significant improvement in pharmacokinetic para meters (AUC, Cmax, tmax, AUMC and MRT) and in bioavailability as compared with marketed product. The fast dissolving films of anti-emetic drugs were found to be a better option in control of nausea and vomiting by way of fast onset of action for patient convenience and compliance.

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