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Anti-emetic drug delivery for cancer patients through electrospun composite nanofibers transdermal patch: *In vitro* study

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ABSTRACT

The objective of the present investigation is to deliver antiemetic GH (Granisetron hydrochloride) drug to cancer patient through nanofibers transdermal patch to overcome the problem of chemotherapy induced post-operative side effects like nausea and vomiting. The biodegradable poly vinylalcohol (PVA) and polyvinyl pyrrolidone (PVP) electrospun composite nanofiber based transdermal patch was developed and anti-emetic drug was loaded by active loading in it. The in-vitro drug release from nanofibers patch demonstrates that there is a controlled release pattern of the drug and release rate is varying with PVP content in the composite nanofiber patch. Also from the data of cumulative drug permeation and steady state flux demonstrates that rate of drug release through membrane and permeation across skin increases with increasing concentration of PVP. The drug release follows Higuchi model of kinetics. While marketed drug tablet follows the zero order kinetic model of drug release. The regression values obtained for both the formulations lie in the range of 0.9484 – 0.951 which suggests the mechanism of drug release is due to the diffusion of embedded drug molecule and erosion of polymer from nanofiber an aqueous medium. Thus the present investigation gives impetus to work in the direction of delivering anti-emetic drug through nanofibers transdermal patch.

Keywords: electrospinning; nanofibers; granisetronhdrochloride; *in vitro* control release.

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Introduction

A perspective of drug delivery systems can be defined as the mechanism to introduce therapeutic agents into the body. Chewing leaves and roots of medical plants are examples of drug delivery from the earliest times. However, these primitive approaches of delivering drugs lacked both consistency and uniformity in drug delivery. This led to the development of different drug delivery methods in the later part of the eighteenth and early nineteenth century. Those methods included pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsions,

suspension, cachets, troches, lozenges, nebulizers, and many other traditional delivery mechanisms. To obtain a given therapeutic response, the suitable amount of the active drug must be absorbed and transported to the site of action at the right time, and the rate of input can be adjusted to produce the concentrations required to maintain the level of the effect for as long as it required **[1]**. The distribution of the drug-to-tissues other than the sites of action and organs of elimination is unnecessary, wasteful, and a potential cause of toxicity. The modification of the means of delivering the drug by projecting and preparing new advanced drug delivery devices can improve therapy **[2, 3]**. The drug delivery system manages the rate of releasing drugs chemically or physically, and it is broadly categorized into sustained and responsive drug delivery depending on the speed of the released amounts by stimuli. The drugs could be loaded into gels, **[4-6]** polymeric micelles **[7-9]** or reservoirs in implant devices **[10, 11]**. It is released through tablets, intravenous injection, transdermal patches and implants **[12]**. To overcome the problem of drug delivery through traditional routes, lot of effort worldwide going on by using nano-scale materials. The nano-scale drug-delivery systems take advantage of the fact that nano-scaled materials can exhibit distinctive physical, electrical and mechanical properties that differ from those observed in the macroscopic and atomic realms **[13]**. Through rational design, nano-scale drug-delivery systems can be developed to combine desirable modules, both biological and synthetic, for various applications, including implantable, inhalable, injectable, and oral and transdermal drug delivery **[14]**. Among the different nanomaterials, electrospun nanofibers endows with a large specific surface area and a porous structure.

Cancer is a class of diseases characterized by out-of-control cell growth. There are more than 100 types of cancer, including breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer, and lymphoma. Symptoms can vary depending on the types. Cancer treatment may include chemotherapy, radiation, and/or surgery. Chemotherapy is the use of medication (chemicals) to treat disease. More specifically, chemotherapy typically refers to the destruction of cancer cells. However, chemotherapy may also include the use of antibiotics or other medications to treat any illness or infection. During the chemotherapy, patient experience some side effect of anticancer drugs such nausea, vomiting, diarrhoea or constipation and physical exertion. To overcome the problem of chemotherapy-induced post-operative side effect, other drug to be given to patient prior to chemotherapy. Granisetron hydrochloride is one of the most widely used 5-HT_3 receptor antagonist, which has beneficial therapeutic effects in the treatment of vomiting and nausea resulting from cancer chemotherapy. It has an improved side effect and tolerability profile, a lower risk of drug interactions and a longer duration of action than other 5-HT_3 receptor antagonists. Unlike all the marketed formulations that use needle to administer this formulation would be "needle free" and hence would provide better "compliance". The injectable formulations requires an expert to administer them with safety and accuracy whereas this formulation would be "simple" and "safe" to administer that too without the help of an expert. So the main objective of the work is to modify the release of Granisetron Hydrochloride (GH) from experimental carrier in order to improve its therapeutic efficacy and also to design a non-invasive carrier system of Granisetron hydrochloride (GH) and hence improve the patient compliance. In this direction in the present study electrospun nanofiber patch from biodegradable polymer for transdermal delivery of antiemetic drug is investigated to improve the therapeutic efficiency of drug. The polyvinyl alcohol (PVA) water soluble polymer composites nanofiber patch is developed with Poly vinylpyrrolidone (PVP), as an aid for increasing the solubility of drug in liquid and semi-liquid.

Experimental

Material and fabrication of nanofibers

The bio-degradable Poly vinylalcohol (PVA) as a hydrophilic polymer soluble in water was procured from CDH, New Delhi. Polyvinyl pyrrolidone (PVP), a common hydrophilic polymer and has strong polar character **[15]**, has good film formation properties which makes it popular for electrospun nanofibers. It is soluble in water and absorbs up to 40% of its weight at ambient conditions **[16]**. PVP has good compatibility and cross linking properties. It is able to complex with a broad variety of compounds. Because of its unique chemical nature, it is biologically inert apart from exerting osmotic activity. A large number of human and animal studies support metabolic inertness and safety of this polymer. PVP K-90 was procured from OIL TEC GmBH, Germany. Granisetron Hydrochloride (GH) was purchased from Eipico laboratories, USA. All solvents used were of analytical grade.

The electrospun nanofiber patch was prepared in the laboratory by using electrospinning equipment ESPIN-NANO **[17, 18]** procured from Physics Instrument Company, Chennai. In our earlier study, we established that 8wt % PVA solution gives the bead free nanofibers with at applied voltage 15 KV **[19]**. Therefore, in this study PVA-PVP nanofibers were prepared by using 8 wt % of PVA and different content of PVP. The different ratio of PVA-PVP was optimized and it was observed that 0.5 and 1.5 wt. % of PVP gives the beads free nanofiber from PVA-PVP solution. The two different type of sample was designated as 0.5PVP and 1.5PVP.

Characterization

The morphology of the electrospun nanofibers and its diameter was examined by scanning electron microscopy (SEM, *EVO M-10, Zeiss*). At least 10 different positions on the nanofiber mat at different magnifications were analyzed for morphology of the electrospun nanofibers patch. The surface roughness of nanofiber and drug loaded electrospun nanofiber composite was observed using atomic force microscope (AFM; SPM-V, Veeco Instruments Inc. USA). The scanning was carried out in semi-contact tapping mode. The Drug GH, composite nanofibers and GH loaded composite nanofibers was characterized by X-ray diffraction (XRD,D8 Advance, Bruker, Japan) in between diffraction angle 5°-50°for their structural properties. The GH, composite nanofiber (PVA-PVP) and Granisetron Hydrochloride loaded composite nanofibers were

characterized by FTIR spectrometer (Nicolet-380, Thermo-USA). In order to obtain FTIR spectra, pellets of KBr and nanofibers was made by compression molding technique.

Percentage moisture absorption and loss in composites nanofibers patch

The nanofibers patch was weighed accurately and placed in the desiccators containing 100 mL of saturated solution of potassium chloride, which maintains 80-90% relative humidity **[20, 21]**. After 3 days, the patch was taken out and weighed. In case of moisture loss measurements the nanofibers patch kept in a desiccators containing anhydrous calcium chloride **[22, 23].** After 3 days, the patch was taken out and weighed. The percentage moisture absorption or loss was calculated using the following formula:

$$(\%)\ \textbf{Moisture Absorption or loss} = \frac{\textbf{Final Weight} - \textbf{Initial weight}}{\textbf{Initial weight}}\ \textbf{x100}$$

Entrapment Efficiency

The entrapment efficiency is ratio of weight of the drug entrapped in nanofiber patch to total drug added. The entrapment efficiency of nanofibers was calculated by drying the drug loaded nanofibers and dried nanofibers put in the simulated saliva solution of pH 6.5 and sonicated for 30 minutes in ultrasonic bath. The amount of drug was calculated by UV analysis of the solutions and was compared with the amount of drug that was loaded during the process of electrospinning of these fibers as per the following Equation;

$$\textbf{Entrapment Efficiency (\%)} = \frac{\textbf{Mass of Maximum Drug Released}}{\textbf{Mass of Total Drug Added}} \times \textbf{100}$$

In vitro drug release from nanofibers patch 0.5 PVP and 1.5 PVP

The in-vitro release studies were performed using franz diffusion **[24, 25]** cell to evaluate the drug release from optimized formulations. The pre-treated cellulose nitrate membrane with pore size of 0.4 µm (Millipore membrane) was used and mounted on the franz diffusion cells with an exposed surface area of 4.9 cm^2.The receptor compartment contained PBS (60 ml) of pH-7.4. The temperature of diffusion media was thermostatically controlled at 37±0.5ºC by surrounding water in the outer jacket and the medium was stirred by magnetic stirrer at 500 rpm. About 4 cm^2 area of nanofiber membrane was cut and applied on the cellulose nitrate membrane which was fixed in between donor and receptor compartment.

The donor well was then capped to prevent evaporation. Samples of 1 mL were taken after 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 18,21 and 24 hours and replaced by an equal volumes of fresh PBS to maintain the sink conditions. After suitable dilutions with PBS the samples withdrawn were analyzed by UV–Vis spectrophotometer at 272 nm against the blank. The results were calculated as the mean of three runs. The obtained data was kinetically related to determine the order of release. The percent drug release was calculated using the calibration curve of the drug in PBS of pH-7.4.

In vitro drug release from marketed tablets

In vitro drug release from marketed tablets (Grandem-1) were carried out using USP XXIV (Type II) dissolution apparatus at 37±0.5°C and 50 rpm speed using 900 ml of phosphate buffer pH 7.4 as dissolution medium. Samples of 1 mL were taken after 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4,4.5, 5, 6, 7, 8, 9, 10, 11 and 12 minutes and replaced by an equal volumes of fresh medium to maintain the sink conditions. After filtration and appropriate dilution, the samples were analyzed at 272 nm for GH by UV-visible spectrophotometer against blank. The amounts of drug present in samples were calculated.

Results and discussion

Morphology of nanofibers patch

The electrospun composite nanofibers are derived from the solution of PVA and PVP. PVP is used as solubility enhancer of drug in the polymer solution so that drug cannot agglomerate during the processing of nanofibers. **Fig. 1** shows the SEM micrograph of the composite nanofiber in which ratio of 0.5PVP. The diameter of the composite nanofibers are in the range of 300-400 nm while on increasing the concentration of 1.5PVP, the diameter of nanofibers decreases to 200-300 nm. This might be due to change in viscosity of the solution due to addition of more contained of solubility enhancer PVP.

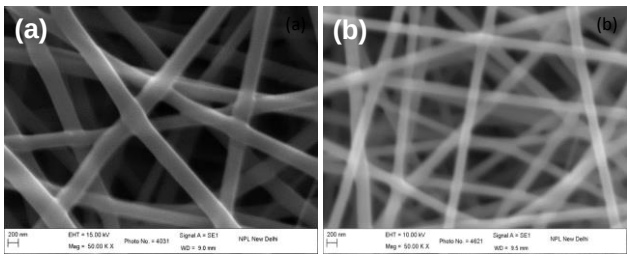

Fig. 1. SEM micrograph of (a) 0.5 PVP and (b) 1.5 PVP composite nanofibers.

Fig. 2 shows SEM micrograph of the GH drug loaded composites nanofibers, in this drug is loaded by active process. The morphology of nanofiber changes on the drug loading, nanofiber diameter increases from 300-400 nm in case of 0.5PVP into 500-600 nm while in case of 1.5PVP fiber diameter increases from 200-300 nm to 400-600 nm. But, there is large variation in nanofiber diameter. Also the morphology of fiber changes in to the somewhat ribbon type with rough surface. This is due to the entrapment of drug molecules in the fibers after active loading and hygroscopic nature of drug entrapped in polymeric change in which solvent is not completed evaporated before they are collected on collector. However, change in the surface morphology of nanofibers has adverse effect on the overall surface roughness of nanofiber patch, which is investigated by atomic force microscopy (AFM). **Fig. 3** shows the AFM images of PVA-PVP and drug loaded PVA-PVP composite nanofibers. The surface area and roughness of PVA-PVP nanofiber patch with 0.5PVP is 525 um^2 and 242 nm and that of drug loaded patch surface area and roughness decreases to 499 um^2 and 228 nm. The decrease in surface area and surface roughness of nanofibers related to

increases in the fiber diameter after drug loading suggest that drug entrapped in the polymeric chain. The AFM and SEM results are in agreement of each other. The interaction of drug with polymeric chain changes the crystalline behavior of the drug and as a results change in the conductivity of solution.

To verify the fact of change in composite nanofiber morphology after drug loading, moisture loss and moisture absorption was measured. It is found that nanofibers patch have moisture loss 5.3% while in drug loaded nanofibers patch have moisture loss 13.3%. The higher value of moisture loss in drug loaded nanofibers patch is due to the fact that during electrospinning drug holds some water molecules which could not evaporate while spinning due to its hygroscopic nature. On the other hand, moisture absorption in nanofibers patch is found to be 59.45% and in drug loaded nanofibers patch is 17.64%. The decrease in moisture absorption in case of drug loaded nanofibers patch could be due to the drug particles have diffused in the nanofibers and filled the pores thereby reducing the effective surface area for moisture absorption. These results are also in the agreement with AFM in which surface area decreases on drug loading. The entrapment efficiency of the drug loaded composite nanofibers, calculated from the formula given in experimental section is 98.7%.

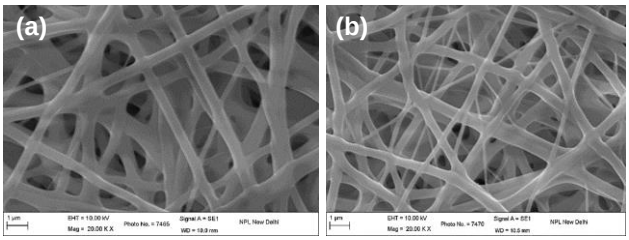

Fig. 2. SEM micrographs of drug loaded (a) 0.5 PVP and (b) 1.5 PVP composite nanofibers patch.

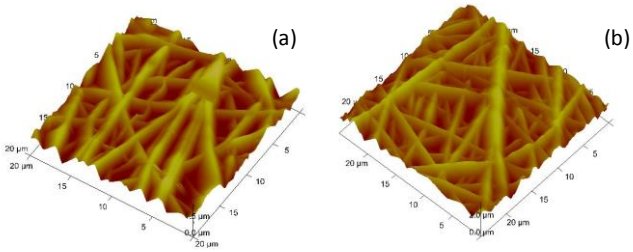

Fig. 3. AFM Images of (a) 0.5PVP and (b) drug loaded 0.5 PVP Nanofibers patch.

XRD and FTIR of nanofibers patch

Fig. 4 shows the XRD spectra of PVA-PVA, Drug loaded nanofiber patch and drug GH. The XRD pattern of pure drug shows several diffraction peaks indicating the crystalline nature of GH. The sharp peaks at diffraction angle of 2θ= 13.91º, 16.77º and 27.27º are observed (Fig. 4, curve c).While in case of PVA-PVP nanofiber patch consist of two prominent peaks at 2θ =19.37º and 29.21º for PVA and PVP respectively (**Fig. 4**, curve **a**). **Fig. 4** (curve b) shows the XRD spectra of GH loaded PVA-PVP nanofiber patch. It is observed that peak registered due to the PVA-PVP are broaden, it appears at 2θ =19.6º and 2θ=29.4º, which are shifted towards higher diffraction angle. While peaks appear due to the drug is low intensity level. This indicates that the drug makes interactions with polymer and as a result crystalline nature of drug has been changed. As a consequence morphology of drug loaded nanofibers changed, which is reported in the earlier section.

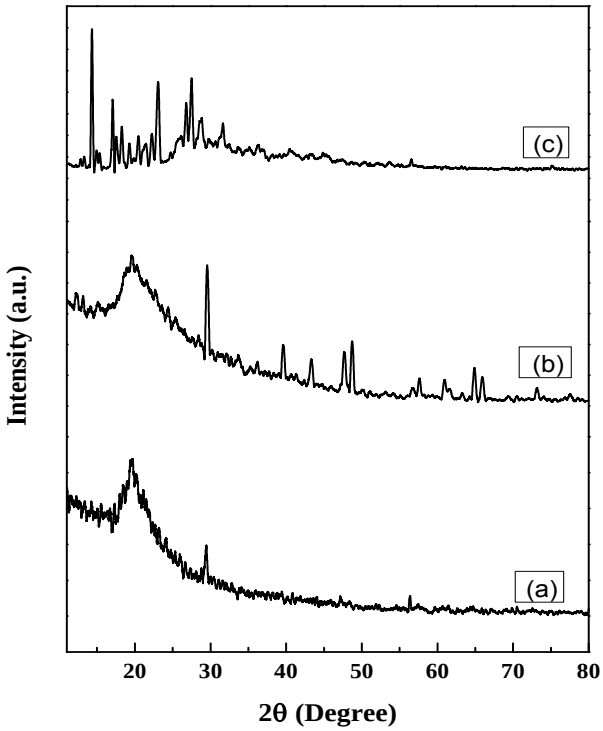

Fig. 4. XRD spectra of (a) PVA-PVP (b) Drug loaded PVA-PVP (c) Drug GH.

Fig. 5 shows the FTIR spectra of PVA-PVP nanofiber, drug GH and drug loaded PVA-PVP nanofiber patch. The GH spectra consist of characteristic absorption peak at 3049 cm^{-1} of C-H vibration, indicating that GH molecule contains aromatic residue. The peak at 2942 cm^{-1} due to C-H of the aliphatic bond of the molecule, peak at 3230 $cm^{-1}$of N-H (Indazole ring). The characteristic peak at 1466 cm^{-1} was due to C-C stretch in ring (aromatic), 1240 cm^{-1} due to C–N stretch aliphatic amines and 1300 cm^{-1} presence of C–N stretch aromatic amines. The C=C absorption peaks at 1648 cm^{-1} suggest that drug molecule contains aromatic moiety along with aliphatic residue, also it contains more than one double bond in the molecule. In case of PVA-PVP nanofibers spectra consist of peaks at 3333 cm^{-1} and 3355 $cm^{-1}$is of hydroxyl groups. The broadening of hydroxyl peak could be due to the formation of a hydrogen bond between PVA and PVP.

A sharp peak at 1660 cm^{-1} is of C=O in PVA–PVP composite nanofiber which is due to of the PVP signature. FTIR spectrum of drug loaded PVA-PVP nanofiber patch reveals the presence of peaks of pure drug and PVA–PVP also. However, small shifts in the peaks can be attributed to the formation of hydrogen bonds between the polymers and the drug.

Drug release from marketed tablet GRANDEM-1

Fig. 6 shows cumulative drug release from marketed drug (Tablet GRANDEM-1) with time. Drug relases started from

the first minutes and relases pattern increase gradually up to 8 min and thereafter increases rapidly. This is due to the dissolution in aqueus medium and with in last two minutes 50 % drug is relased from the tablet.

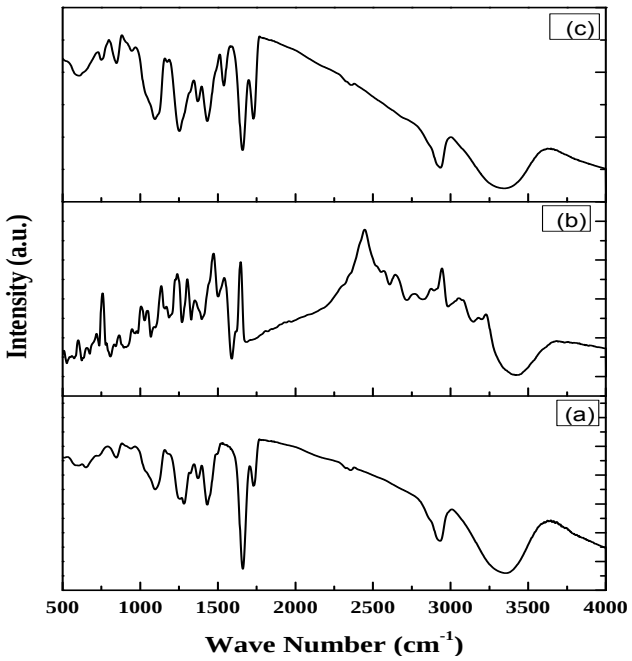

Fig. 5. FTIR spectra of (a) PVA-PVP nanofiber (b) Drug GH (c) Drug loaded PVA-PVP nanofiber patch.

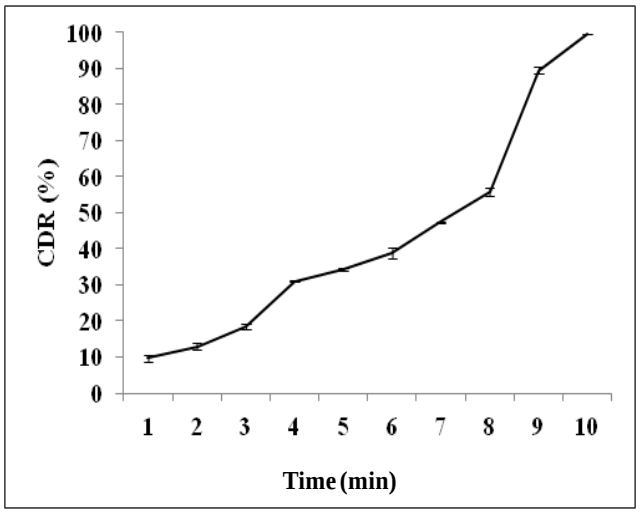

Fig. 6. Cumulative drug release from marketed drug.

In order to undertsand the kinetics of drug release from marketed (GRANDEM-1) tablet differnt kinetic models zero order, first order, Hixson-crowell and Higuchi are studied (**Fig. 7**). The tablet follow zero order kinetic andregression (r^2)value is 0.907. This described the drug relase from the tablet is due to the dissolution.

In vitro drug release from composite nanofibers patch

The In-Vitro drug release studies of composite nanofiber formulation are carried out byfranz diffusion cell. The interference studies are also done prior to the selection of physiological media in order to ascertain that the polymer do not show interference with the analysis of drug. UV scans of 0.1% drug, 0.1% polymers and combination of polymers and drug (0.1% each) revealed that the drug exhibited λmax at 272 nm in PBS with pH 7.4 and polymer does not show absorbance at the same wavelength. Analysis of in vitro permeation parameters i.e., cumulative drug permitted per unit area and steady state flux, is depicted in **Table 1**.

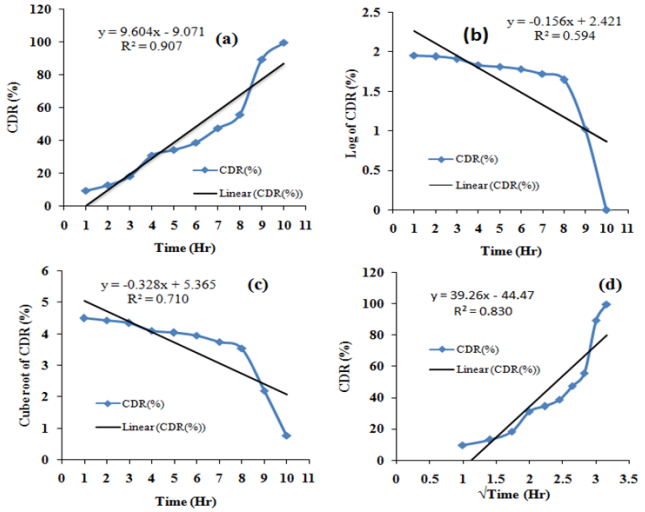

Fig. 7. Kinetics of drug release from marketed (GRANDEM-1) (a) Zero order (b)First order (c) Hixon-crowell and (d) Higuchimodel.

Table 1. In vitro permeation parameters.

Formulation Code	CDP^ (µg/cm²)	Flux (µg/cm²/h)
0.5 PVP	1596.42	308.47
1.5PVP	2320.4	406.61

CDP^ = Cumulative drug permeated in 2 hours.

The steady state flux measured rate at which a molecule passes through the membrane barrier in to physiological media in a given period. The comparative flux values for 0.5PVP composite nanofibers patch is 308.47µg/cm^2/h while that of 1.5PVP is 406.61µg/cm^2/h. The lower value of CDP and flux in case of 0.5PVP nanofibers patch could be due to the less % of hydrophilic character as compared to 1.5PVP nanofiber patch. This demonstrates that rate of drug release through membrane and permeation across skin increases with increasing concentration of hydrophilic polymer.

The % cumulative drug release (CDR) from 0.5PVP and 1.5PVP drug loaded composite nanofibers patch is illustrated in **Fig. 8**. It is observed that CDR in early 0.5 hr is 13 % in 0.5PVP and 17.83 % in 1.5PVP nanofiber patch. The % CDR in first 2 hrs from 0.5PVP and 1.5PVP is 41.8% and 50.8% respectively. The cumulative drug release is continues with increasing the time and rate of CDR is higher in case of higher hydrophilic polymer content based nanofibers patch (1.5PVP). After nine hr of time, maximum CDR 94.43 % in 1.5PVP and 81.3 % in 0.5 PVP base patch. After 24hr, 99.43 and 97.46 % of CDR in case of 0.5PVP and 1.5 PVP nanofiber patch. The higher

rate of CDR in case of 1.5PVP base nanofiber patch is attributed to the leaching of the soluble component, which leads to the formation of pores and thus a decrease in the mean diffusion path length of drug molecules to release into the dissolution medium. This leads to higher dissolution rate in case of 1.5PVP based nanofiber patch. Substances such as PVP act as antinucleating agents that retard the crystallization of a drug. Thus they play a significant role in improving the solubility of a drug in the matrix by sustaining the drug in an amorphous form so that it undergoes rapid solubilization by penetration of the dissolution medium. The release of drug is associated with the penetration of water into the fibres and the dissolution of drug in aqueous medium. The smaller the fiber diameter, the shorter the time needed for water to penetrate in the nanofibers (1.5PVP nanofibers patch) and hence the higher rate of drug release. But it is interesting to note in case of 0.5PVP patch, the drug release rate is comparatively lower down after 2hr and it shows somewhat sustained type drug release.

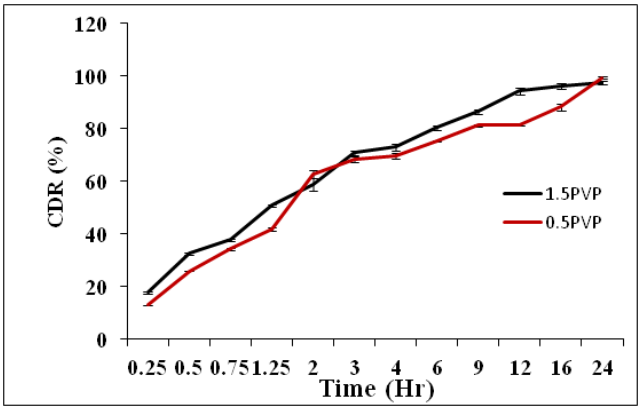

Fig. 8. Cumulative drug release (CDR) from 0.5PVP and 1.5PVP nanofibers patch with time.

If compared the CDP and CDR for initial two hr is higher in case of 1.5 PVP based composites nanofiber patch.

In this study the drug release initially is due to desorption of embedded drug molecules from nanopores of the nanofibers, which is the primary pathway as well as the rate limiting step. Later on, diffusion of encapsulated drug molecule is from the nanofibers patch into the surrounding aqueous medium, which is due the hydrophilic nature of nanofiber patch. In this water molecules permeate/penetrate into the nanofiber patch. As a consequence, polymer molecules get hydrolyzed and erosion of the polymers. As a result hydrophilic polymers based nanofibers patch yielded in to controlled drug release delivery.

In order to completely understand the kinetics of drug release, it is essential to apply the different kinetic models including zero order, first order, hixson-crowell and higuchi curves. The value of regression coefficient (r^2) from these curves represents the extent up to which a particular model is being followed. All these models for 0.5 PVP and 1.5 PVP formulations are given in **Fig. 9** and **10**.

The cumulative amount of drug permeated per square centimeter of patches through cellophane is plotted against time and fitted to first and higuchi kinetic model. It is observed that the release profile of GH drug from the 0.5 PVP nanofiber patch (r2 = 0.9484 for Higuchi) indicated that the permeation of the drug from the nanofiber membrane is governed by a diffusion mechanism whereas first order and higuchi model are best fitted in case 1.5 PVP nanofibers patch with r^2 value 0.951(**Fig. 9** and **10**).

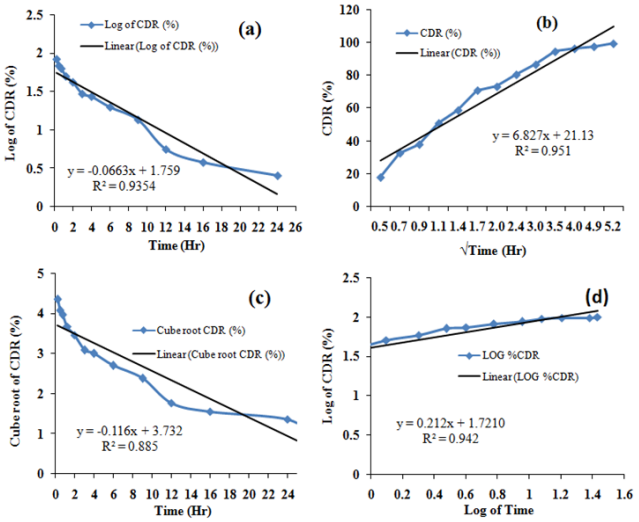

Fig. 9. Kinetic model for 0.5PVP nanofiber patch (a) First order (b) Higuchi and (c) Hixon-crowell (d) Krosmeyer- peppas model.

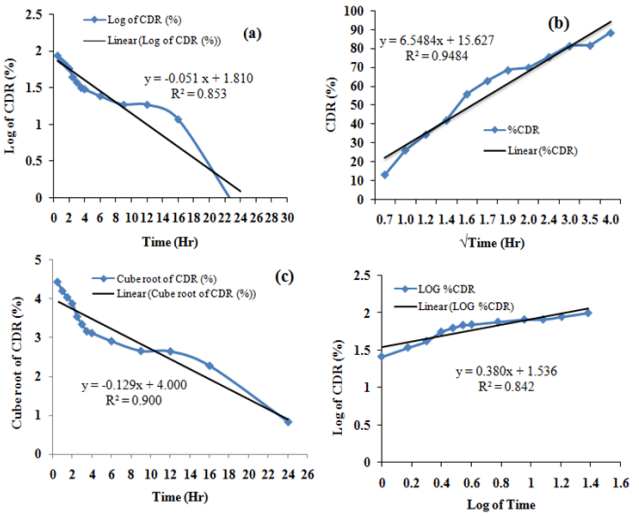

Fig. 10. Kinetic model for 1.5 PVP nanofiber patch (**a**) First order (**b**) Higuchi (**c**) Hixon-crowell and (**d**) Krosmeyer-peppas.

The drug release kinetics is studied by using different drug release kinetic models. The regression values obtained from different models clearly indicate that the kinetics of drug release followed Higuchi model. The Higuchi model suggests the kinetics of drug release by diffusion, which is clearly justified by the pattern of drug release obtained. The regression values obtained for both the formulations lie in the range of 0.9484 – 0.951 which suggests the mechanism of drug release by combination of both erosion as well as diffusion. The release of drug by diffusion through the polymer matrix and the drug release is not zero-order. The release of drug is associated with the penetration of water into the fibres and the dissolution of drug in aqueous medium. The smaller the fibre diameter, the shorter the time needed for water to penetrate in the nanofibers. This could be one reason for the high release rate.

Conclusion

In the present investigation, explores the possibility of anti-emetic (Granisetron hydrochloride) drug delivery to cancer patient through nanofibers transdermal patch to overcome the problem of chemotherapy-induced post-operative side effect. The anti-emetic drug is loaded by active loading in PVA-PVP composite nanofibers patch. It is observed that addition of PVP in the PVA solution control morphology of nanofiber drawn by electrospinning technique. After drug loading, surface area and roughness of the nanofibers patch decreases. The in-vitro activity provided a controlled release pattern of the drug from nanofibers patch and release rate is varying with PVP content in the composite nanofiber patch. Also from the data of cumulative drug permeation and steady state flux demonstrates that rate of drug release through membrane and permeation across skin increases with increasing concentration of PVP. The drug release follows Higuchi model of kinetics. While marketed drug tablet follows the zero order kinetic model of drug release. The regression values obtained for both the formulations lie in the range of 0.9484 – 0.951 which suggests the mechanism of drug release by combination of both erosion as well as diffusion. The study clearly brings out the fact that, if we can control the morphology of nanofiber by using hydrophobic polymer, it can certainly possible to deliver anti-emetic drug by control and sustained release pattern. Thus the present investigation gives impetus to work in the direction of delivering anti-emetic drug through nanofibers transdermal patch.

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