New drug application of paclitaxel: results and discussion

The present research work is an attempt made to design and development of a new drug application for of Paclitaxel sustained release microspheres by using ionic Gelation and solvent evaporation methods is to achieve first order to improve bioavailability and reduce side effects of paclitaxel. For this purpose different polymers like HPMC K100, EUDRAGIT RS100, ETHYL CELLULOSE, and in combination were used. Based on the above investigational reports. I concluded the following results and discussions.

7. 1. Preformulation Studies:

The reports indicate the exhibit good and passable flow properties. So there is no need to improve the flow of the powder. The regression value obtained from analytical method development in buffer media is 0. 999. so, the drug is exhibiting linearity in concentration 2ug to 10 ug. The FT-IR spectral studies indicate good stability and no chemical interaction between the drugs and excipients used.

7. 1. 1. Identification of paclitaxel

In identification of API it was found that paclitaxel was soluble in methanol, ethanol, acetone

7. 2 Stability studies

7. 2. 1. – Photo stability:

When paclitaxel was exposed to light for a period of 2 months (60days) it was found that 0. 2% of the drug was degraded.

7. 2. 2. Acidic degradation

When the drug was exposed in acidic medium 0. 1N HCL for a period of 24 hrs , it was found that there is no degradation of the drug in alkaline mediums showing 100% stability in the acidic medium.

7. 2. 3. Alkaline degradation:

When the drug was exposed in different alkaline mediums like phosphate buffer 7. 4 for a period of 24 hrs, it was found that there is no degradation of the drug in alkaline mediums showing 100% stability in alkaline medium.

7. 2. 4 Temperature stress conditions:

When the drug was exposed to different temperatures (0 ^{0}C, 10 ^{0}C, 20 ^{0}C, 30 ^{0}C, 35 ^{0}C, 45 ^{0}C and 50 ^{0}C, 60 ^{0}C) for a time period of 1hr, 3hr, 6hr, 12hr, 24hr, was found that there is no degradation of the drug in Temperature stress conditions.

7. 3. Solubility studies:

Solubility of paclitaxel:

Paclitaxel is soluble in methanol, ethanol, acetone etc;. paclitaxel is in soluble in water

s. no	Solubility media	Descriptive term
1	Water	Practically insoluble

2	Methanol	Soluble
3	Ethanol	Soluble
4	DMSO	Soluble
5	ph 7. 4 buffer	Sparingly soluble

Melting Point:

It was also found Melting point of paclitaxel was 216 ^{0} c,

Density:

On analyzing for density it was found that paclitaxel showed bulk density value 0. 593gm/ml and tapped density value 0. 514 gm/ml,

Carr's Index:

The value of Carr's Index for 13. 32 and drugs showed good flow characteristics

Compressibility Index:

The value of Compressibility Index for was 14. 28, and drugs showed good characteristics.

Hausner's ratio:

The value of Hausner's ratio for paclitaxel was 1. 16 drugs showed good flow characteristics.

Angle of Repose:

The studies on angle of repose showed that was 26. 83 values indicated good flow properties.

Stability studies

FTIR studies:

From the FTIR spectra, it was concluded that similar characteristic peaks with minor difference for the drug and their formulation. Hence, it appears that there was no chemical interaction between the drugs and excipients used. The IR Spectra of paclitaxel with HPMC – K100, Eudragit Rs100, Ethyl cellulose were shown in figs. The following peaks were observed in as well as paclitaxel with excipients.

EVALUATION OF MICROSPHERES:

Determination of percentage yield:

The percentage yield was estimated from all the 18 formulations the results obtained between the range 86. 03 %to 76. 56%. all the formulation was found within the limits.

Drug entrapment efficiency:

The drug entrapment of all formulation of paclitaxel microspheres varied from 86. 19 to 67. 38

Particle size analysis:

The particle size of the microspheres of the paclitaxel formulations varied from 836 µm to 191µm.

In vitro drug release studies:

The formulation F1, F4, F7 contains HPMC K 100, Eudragit Rs100, Ethyl cellulose, as a polymers in 1% concentration prepared by ionic gelation method. These formulations subjected to drug release studies in 7. 4 ph phosphate buffer as a dissolution medium.

The formulation F1 that containing 1% HPMC K100, amount of the drug is release 36. 92% in 48 hrs. . And the formulation F4 containing 1% Eudragit Rs 100, amount of the drug release 43. 92 in 48hrs, The formulation F7 containing 1 % Ethyl cellulose , amount of the drug release 68. 96 in 48hrs.

The formulation F2 that containing 20mg HPMC k 100, 10mg, Eudragit Rs 100, amount of drug is release 41. 73 in 48hr. the formulation F3containing 10mg Ethyl cellulose, 20mg HPMC K 100, amount of drug release 46. 98 in 48 hrs. the formulation F5 containing 20mg Eudragit Rs100, 10mgHPMC K 100 amount of drug release 50. 24 in 48 hrs. the formulation F6 containing 20mg Eudragit, 10mgEthyl cellulose amount of drug release53. 28 in 48hrs. The formulation F8 that containing 10mg HPMC k 100, 20mgEthyl cellulose, amount of drug is release 63. 24 in 48hrs, the formulation F9containing

20mgEthyl cellulose, 10mg Ethyl cellulose, amount of drug release 56. 23 in 48 hrs.

From formulations F1 to F9 shows cumulative percentage drug release in 48 hr in between 36. 92% to 68. 96%.

The formulation F10, F13, F16 contains HPMC K 100, Eudragit Rs100, Ethyl cellulose, as a polymers in 1% concentration prepared by solvent evaporation method. These formulations subjected to drug release studies in 7. 4 ph phosphate buffer as a dissolution medium.

The formulation F10 that containing 1% HPMC K100, amount of the drug is release 42. 28% in 48 hrs. . And the formulation F13 containing 1% Eudragit Rs 100, amount of the drug release 49. 32 in 48hrs, The formulation F16 containing 1 % Ethyl cellulose , amount of the drug release 79. 42in 48hrs.

The formulation F11 that containing 20mg HPMC k 100, 10mg, Eudragit Rs 100, amount of drug is release 46. 43 in 48hr. the formulation F12containing 10mg Ethyl cellulose, 20mgHPMC K 100, amount of drug release 53. 67 in 48 hrs. The formulation F14 containing 20mg Eudragit Rs100, 10mgHPMC K 100 amount of drug release 55. 86 in 48 hrs. the formulation F15 containing 20mg Eudragit, 10mgEthyl cellulose amount of drug release59. 11 in 48hrs. The formulation F17 that containing 10mg HPMC k 100, 20mgEthyl cellulose, amount of drug is release 74. 82 in 48hrs. the formulation F18containing 20mgEthyl cellulose, 10mg Ethyl cellulose, amount of drug release 65. 24 in 48 hrs.

From formulations F10 to F18 shows cumulative percentage drug release in 48 hr in between 42. 28% to 79. 42%.

The release profiles showed a characteristic initial burst release followed by a lag period and further initiation of sustained release. After the initial lag, a nearly linear and continuous release was observed over 48 hr Comparison of *in-vitro* drug release profiles for all formulations F1to F9 and F10 to F18 are shown in Fig (7, 8) and the data is shown in Tables (13, 14).

Effect of method of preparation

- Ionic gelation
- solvent evaporation

1. On particle size :

From formulations F1to F9 are by ionic gelation method.

Spheres obtained are larger than desired particle size range i. e 609-875. μm.

formulations F10 to F18 are by solvent evaporation, are in desired particle size range i. e

191-303 μm.

So that Spheres obtained are smaller than by ionic gelation method.

2. On Drug release:

Drug release is sustained in formulations prepared by solvent evaporation than with ionic gelation.

Therefore from above results solvent evaporation method is selected.

Effect of polymers

HPMC K100, Ethyl cellulose, Eudragit RS100 are three different polymers used as sustained release polymers.

Formulations F1, F4, F7 by ionic gelation where as F10, F13, F16, by solvent evaporation are with single polymer respectively.

Remaining all formulations are combination of two each polymers of respective ratios

HPMC K100 is hydrophilic, Ethyl cellulose is hydrophobic nature. Combination of Hydrophilic and Hydrophobic polymers is tested at different ratios to determine effect on sustained drug release

Also HPMC K100 with coating polymer Eudragit RS 100 combination is tested at different ratios

Among all these , F10 i. e, with single polymer HPMC K100 by solvent evaporation method shows desired drug release compared to combination of polymers.

Therefore it is concluded that there is no effect of combination of polymers on drug release of paclitaxel microspheres.

Kinetics of drug release from optimized formulation

The kinetics of the drug release was evaluated by drug release rate models namely zero order, First order. The mechanisms of drug release was evaluated by First order drug release. The dissolution kinetics data was defected in table 15 and the comparative dissolution profile was given in the figure 9 .

The drug release followed zero order kinetics in all polymers employed. The graph drawn in between time Vs cumulative % drug release show in figure 12 to 15.