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# Design and development of Pacritinib polymer coated particle for sustained release tablet.

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***Abstract***
*Sustained release drug delivery systems designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time from two decades or more. Development of a successful sustained release formulation depends upon a number of factors: from the selection of potential drug candidates to the optimization of process variables involved in the preparation. There have been significant advances in the area of sustained release with the introduction of new polymer and co polymers. Currently available polymers for controlled release can be classified into four categories: chemically controlled systems, diffusion controlled systems, magnetically controlled systems, and solvent activated systems. Ethylcellulose is the most commonly used polymer for sustained release preparation. Cancer is the leading cause of mortality and morbidity after the heart diseases across the globe which affected 9.3 million lives in year 2018. Sustained release and extended-release dosage forms have the advantage of better patient compliance and low dosing frequency. Although they have a potential threat of dose dumping, several attempts have been made by pharmaceutical scientists to develop sustained and extended-release drug delivery systems. Pacritinib citrate is a drug of choice for myelofibrosis. It is a macrocyclic protein kinase inhibitor. Myelofibrosis is a rare blood cancer where scar tissue forms in your bone marrow. It's a type of chronic leukemia that involves too many abnormal blood cells being made. Eventually, these cells can replace normal cells. Treatment goals mainly involve managing symptoms and conditions that arise, including anemia and an enlarged spleen. The present work involves formulation of Sustained release tablets of Pacritinib citrate using micro fluidization technique to reduce particle size of pacritinib citrate and Ethyl cellulose coating granulation method which were evaluated for the preparation of tablets to control the release. The formulated tablets were subjected to various evaluation tests like weight variation, hardness, assay, dissolution tests. Finally, it was concluded that the N9 batch shows the best results, amongst all formulated batches.*

***Keywords:*** *Extended-release, systems, Sustained release systems, Pacritinib citrate, myelofibrosis , Fluidized bed processor*

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## I. Introduction

Cancer is the leading cause of mortality and morbidity after the heart diseases across the globe which affected 9.3 million lives in year 2018. Cancer represents a class of disorders characterized by abnormal rapid division of cells in the human body which lead to death. Cancer commences with selective DNA mutations which facilitate the cellular growth and proliferation. These cells are born, invade, destroy normal cells, and produce an imbalance in the body. In normal cells, mutations are repaired in the DNA milieu, in contrast, the cancerous cells lose the ability to repair itself. Global burden on primary causes of cancer death is due to tobacco use, alcohol use, obesity, low intake of dietary fibre, excessive eating of red meat, smoking, higher consumption of salt and saturated fats, ionizing and non-ionizing radiation, reduced ingestion of fruits and green vegetables, and numerous carcinogenic infectious agents.[1-4]

Over the past 40 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of the sustained or controlled release drug delivery systems.[5] The attractiveness of these dosage form is due to awareness of toxicity and other properties of the drugs when administrated or applied by conventional method in the form of tablet capsule, injectable, ointment etc. Usually,

conventional dosage form are required to be administrated 2-3 times a day and produce wide ranging fluctuation in drug concentration in blood stream and tissues with consequent undesirable toxicity and poor efficiency[1]. These few reason as well as factors such as unpredictable absorption and kinetics lead to the concept of oral controlled drug delivery systems.[7-9]

## II. Materials and Methods:

The list of materials procured from various sources have been enlisted in Table 1.

**Table 1:** List of materials procured

| Materials | Source |
|---|---|
| Pacritinib Citrate | BOC Sciences |
| Ethyl cellulose | Degussa |
| Microcrystalline cellulose 112 | Dupont |
| Colloidal silicon dioxide (Aerosil) | Madhusilica |
| Maize Starch | Gujrat starch |
| Magnesium Stearate | Nikitha Pharma |
| Purified water | ALS pvt ltd |
| HPMC E 15 | Colorcon Asia |
| Acetone | Loba chemi |

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is first step in the rational development of dosage forms. Preformulation Study of Pacritinib Citrate included various test like Organoleptic properties, Particle size and surface area, Crystallinity and Polymorphism, Solubility and Drug, Excipient compatibility study.[10]

The process for formulation of Pacritinib Citrate was developed in a systematic way. Trials were taken by microfludization with Hydrophilic polymers of different concetration. The particle size of the pacritinib citrate achieved By this method, properties of the formulation components are modified to overcome solubility issue. Pacritinib Citrate having a high dosage and low soluble and solubility must be achieved by microfluidization for suitable dissolution for complete release. In this process, different concentration of polymer in 1% to 2 % required imparting adequate particle size and solubility is found much high than that of the unprocessed pacritinib citrate needed to produce a tablet by wet granulation method or dry granulation method .[11-14] The various steps of formulation trials N1 to N10 are given in Table 2.

**Table 2:** The various steps of formulation trials N1 to N10

| S.No. | Mfg Steps | N1 | N2 | N3 | N4 | N5 | N6 | N7 | N8 | N9 | N10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1.** | **Nano suspension preparation** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **2.** | **Dry sifting** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **3.** | **Mixing** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **4.** | **Polymer solution preparation** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **5.** | **Spray drying using nano suspension** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| | **Spray drying using Ethyl cellulose solution** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **6.** | **Sifting of dry granules** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **7.** | **Sifting** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **8.** | **Lubrication** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **9.** | **Compression** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

**Formulation of batches:**

The various formulations are provided in Table 3.

Table 3: The various steps of formulation trials N1 to N10

| Ingredients (mg) | N1 | N2 | N3 | N4 | N5 | N6 | N7 | N8 | N9 | N10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Ganulation process** | **Dry granulation** | | | | | | | | | |
| Pacritinib Citrate | 400 | 400 | 400 | 400 | 400 | 400 | **400** | 400 | 400 | **400** |
| HPMC E 15 | 20 | 20 | 20 | 20 | 20 | 15 | **15** | 15 | 15 | **15** |
| Purified water | QS | QS | QS | QS | QS | QS | QS | QS | QS | QS |
| Ethyl cellulose 20 cps IP/BP | 10 | 20 | 30 | 40 | 50 | 55 | **65** | 75 | 80 | **85** |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Acetone | QS | QS | QS | QS | QS | QS | QS | QS | QS | QS |
| M.C.C.P pH112 IP/BP | 479.5 | 479.5 | 479.5 | 479.5 | 479.5 | 384.5 | **384.5** | 384.5 | 384.5 | **384.5** |
| Colloidal silicon dioxide IP/BP | 4 | 4 | 4 | 4 | 4 | 4 | **4** | 4 | 4 | **4** |
| Maize Starch IP/BP | 33 | 33 | 33 | 33 | 33 | 33 | **33** | 33 | 33 | **33** |
| Lactose IP/BP | 99.5 | 89.5 | 79.5 | 69.5 | 59.5 | 154.5 | **144.5** | 134.5 | 129.5 | **124.5** |
| Magnesium Stearate IP/BP | 4 | 4 | 4 | 4 | 4 | 4 | **4** | 4 | 4 | **4** |
| TOTAL | **1050mg** | **1050mg** | **1050mg** | **1050mg** | **1050mg** | **1050mg** | **1050mg** | **1050mg** | **1050mg** | **1050mg** |

**# all Units are in mg / tablet**

## III. Results:

After the evaluation of all trials, the results of physical properties of granules are provided in Table 4, Physical Parameters of Pacritinib Citrate Sustain Release Tablets Trial Batches in Table 5 and Chemical Evaluation of Pacritinib Citrate SR Tablets Trial Batches tabulated in Table 6 respectively. The Figure 1 shows the dissolution profile of all formulations.

**Table4:** Physical Properties of Blends of all Trial Batches

| Trial | Bulk Density (gm / cc) | Tapped density (gm / cc) | % Compressibility Index | Hausner Ratio |
|---|---|---|---|---|
| N1 | 0.71 | 0.72 | 1.40 | 1.01 |
| N2 | 0.71 | 0.73 | 2.85 | 1.02 |
| N3 | 0.68 | 0.76 | 9.72 | 1.10 |
| N4 | 0.69 | 0.75 | 6.84 | 1.07 |
| N5 | 0.73 | 0.74 | 1.40 | 1.01 |
| N6 | 0.70 | 0.78 | 9.72 | 1.10 |
| N7 | 0.73 | 0.81 | 9.8 | 1.10 |
| N8 | 0.71 | 0.75 | 4.2 | 1.04 |
| N9 | 0.72 | 0.76 | 5.55 | 1.05 |
| N10 | 0.71 | 0.75 | 5.63 | 1.05 |

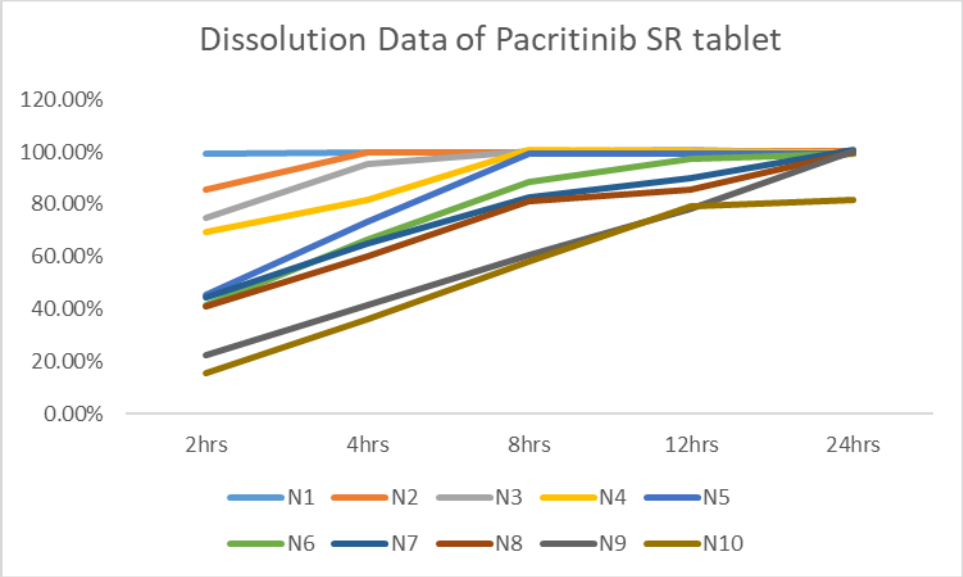
**Table5:** Physical Parameters of Pacritinib Citrate Sustain Release Tablets Trial Batches

| Trial | Weight Variation (mg) | Thickness (mm) | Hardness ($kg/cm^2$) | Friability (%) |
|---|---|---|---|---|
| N1 | 1050 ± 2 % | 5.8 ± 0.2 | 10-14 | 0.75 |
| N2 | 1050 ± 2 % | 5.8 ± 0.2 | 11-12 | 0.63 |
| N3 | 1050 ± 2 % | 5.8 ± 0.2 | 10-13 | 0.66 |
| N4 | 1050 ± 2 % | 5.8 ± 0.2 | 10-12 | 0.59 |
| N5 | 1050 ± 2 % | 5.8 ± 0.2 | 8-11 | 0.74 |
| N6 | 1050 ± 2 % | 5.8 ± 0.2 | 9-12 | 0.59 |
| N7 | 1050 ± 2 % | 5.8 ± 0.2 | 9-11 | 0.45 |
| N8 | 1050 ± 2 % | 5.8 ± 0.2 | 9-11 | 0.65 |
| N9 | 1050 ± 2 % | 5.8 ± 0.2 | 10-12 | 0.68 |
| N10 | 1050 ± 2 % | 5.8 ± 0.2 | 12-14 | 0.64 |

**Table6:** Chemical Evaluation of Pacritinib Citrate SR Tablets Trial Batches

| Trial | Assay (%) | % of Drug Released (After 2 hrs) | % of Drug Released (After 4 hrs) | % of Drug Released (After 8 hrs) | % of Drug Released (After 12 hrs) | % of Drug Released (After 24 hrs) |
|---|---|---|---|---|---|---|
| N1 | 99.56% | 99.21% | 100.01% | 100.02% | 100.34% | 99.98% |
| N2 | 99.67% | 85.32% | 99.56% | 99.96% | 100.12% | 100.29% |
| N3 | 99.27% | 74.65% | 95.35% | 100.41% | 100.85% | 99.11% |
| N4 | 99.15% | 69.29% | 81.41% | 100.87% | 100.26% | 99.93% |
| N5 | 99.01% | 45.31% | 73.29% | 99.26% | 99.23% | 99.14% |
| N6 | 99.09% | 41.23% | 66.32% | 88.32% | 97.35% | 99.36% |
| N7 | 99.95% | 44.47% | 64.98% | 82.52% | 89.88% | 100.54% |
| N8 | 99.29% | 40.86% | 60.00% | 81.09% | 85.36% | 99.57% |
| N9 | 99.54% | **22.23%** | **41.62%** | **60.69%** | **78.18%** | **100.23%** |
| N10 | 99.57% | **15.68%** | **35.79%** | **57.94%** | **78.96%** | **81.61%** |

Fig 1: Dissolution of all formulations




## IV. Discussions:

1. The results of physicochemical evaluation of tablets are given in table no 5. The tablets of different batches were found uniform with respect to thickness (5.8 ± 0.2mm), diameter (16.0 X 6.1 mm) and hardness (8 to 14 kg/cm$^2$)
2. The friability (%) and weight variation of different batches of tablets were found within the prescribed limits. Hence, the tablets containing drug, HPMC, ethyl cellulose, Lactose, Maize starch,and Magnesium Stearate, colloidal silicon dioxide, Microcrystalline cellulose could be prepared satisfactorily by spray drying. Acetone and water will evaporated during process.
3. The results of *in vitro* drug release studies in phosphate buffer pH 7.5 (from 2 to 24 h) are presented in Fig. 1 It was expected that the optimum formulation of this study which matches the dissolution profile of 2 tablet would produce similar in vivo activity. Hence the release profiles of the drug from all the prepared formulations were compared with that of the marketed tablet.
4. The *in vitro* drug release profiles of other 9 developed formulations did not match with that of marketed 2 immediate release formulation, which demonstrated the need for further development of an optimized other formulation.
5. The overall drug release was less than that of marketed product, which might be due to the presence of ethyl cellulose alone to form a diffusion control system to retard pacritinib citrate.
6. Formulations of ethyl cellulose were selected for further development process because coating of ethyl cellulose showed a rapid drug release in lower concentration that is from 10 to 65 mg per tablet 75 mg per tablet and 85 mg per tablet shows retard to give Controlled drug release. Formulations with ethyl cellulose 10mg showed a rapid drug release and 85mg gives lower drug release in end point of dissolution.
7. Diluents like Lactose, Micro crystalline cellulose and Maize starch were used for reducing the rigidity of swollen matrix in addition to increase the flow ability of Pacritinib Citrate.
8. Among these tablets, the release profile of Batch no.N9 was found to be nearly matching to that of the 2 nos of marketed tablet.the cumulative release drug comparatively controlled from the initial interval. In the further development process formulation Batch no.N8 was modified by increasing concentration of ethyl cellulose to 80mg. Compared to other prepared formulations, Batch no.N9 released controlled amount of drug in the initial hours of dissolution study. The results indicated that Batch no.N9 released the drug in a manner, follow first order release kinetics. Hence Batch no.N9 can be considered as better formulation among the prepared sustained release tablets.
9. The similarity in the release profiles of marketed 2 nos tablet and formulation Batch no.N9 was compared by making use of "Model dependent approach". A simple model dependent approach used.
10. For Batch no. N9 formulation, when compared with marketed tablet, follow first order kinetics. It also show a low level of impurity that is 0.02% individual impurities and 0.05% total impurity.
11. Hence the optimized tablet Batch no.N9 behaves similarly as that of marketed tablet with respect to drug release patterns and thus it was selected for further *in vivo* studies can be replace current market sample as once daily dose.

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