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Design and development of a novel formulation of pacritinib for treatment of adults intermediate and high risk myelofibrosis with low platelet count

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Abstract
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 formyelofibrisis. 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 by using various hydrophilic polymers like HPMC 15 CPS, HPMC K4M, HPMC K15M CR, HPMC K1000M CR and Ethyl cellulose 20cps. Dry granulation and wet granulation techniques were evaluated for the preparation of tablets. The formulated tablets were subjected to various evaluation tests like weight variation, hardness, assay, disintegration and dissolution tests. Finally, it was concluded that the F3 batch shows the best results, amongst all formulated batches.

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

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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 such as chronic infections.[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] Theattractiveness of these dosage form is due to awareness of toxicity and other properties of the drugs when administrated or applied by conventional method inthe form of tablet capsule, injectables, ointment etc. Usually, conventional dosageform are required to be administrated 2-3 times a day and produce wide rangingfluctuation in drug concentration in blood stream and tissues with consequentundesirable toxicityand poor efficiency[1]. These factors 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	Avyukta Pharmachem
HPMC 15CPS	Colorcon

HPMC K4M (Methocel K4M)	Colorcon
HPMC K15M CR (Methocel K15M)	Colorcon
HPMC K100M CR (Methocel K100M)	Colorcon
Ethyl cellulose 20cps	Degussa
Microcrystalline cellulose	Dupont
Colloidal silicon dioxide (Aerosil)	Madhusilica
Maize Starch	Gujrat starch
Magnesium Stearate	Nikitha Pharma
PEG-6000	Indian Glycol

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 wet granulation tableting process and dry granulation process with Hydrophilic polymers of different grade. The cohesiveness and compressibility of powders is improved due to the added binder that coats the individual powder particles, causing then to adhere to each other so that they can be formed into agglomerates called granules.By this method, properties of the formulation components are modified to overcome their tabletting deficiencies.Pacritinib Citrate having a high dosage and poor flow and / or compressibility must be granulated by the wet method or dry granulation to obtain suitable flow and cohesive for compression. In this process, the proportion of the binder required imparting adequate compressibility and flow is much less than that of the dry blend needed to produce a tablet by direct mixing compression.[11-14]The various steps of formulation trials F1 to F10 are given in Table 2.

Table 2: The various steps of formulation trials F1 to F10

S.No.	Mfg Steps	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Dry sifting	√	√	√	√	√	√	√	√	√	√
2.	Dry Mixing	√	√	√	√	√	√	√	√	√	√
3.	Binding Solution Preparation	√	√	√	√	√	-	-	-	-	-
4.	Wet granulation	√	√	√	√	√	-	-	-	-	-
5.	Wet milling	√	√	√	√	√	-	-	-	-	-
6.	Drying	√	√	√	√	√	-	-	-	-	-
7.	Sieving and Milling	√	√	√	√	√	-	-	-	-	-
8.	Lubrication	√	√	√	√	√	√	√	√	√	√
9.	Compression	√	√	√	√	√	√	√	√	√	√

Formulation of batches:

The various formulation steps are provided in Table 3.

Table 3: The various steps of formulation trials F1 to F10

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ganulation process	Wet granulation					Dry granulation				
Pacritinib Citrate	400	400	400	400	400	400	400	400	400	400
Methocel K4M IP/BP	44.5	--	---	---	---	44.5	--	---	---	---
Methocel K15M IP/BP	---	44.5	---	---	---	---	44.5	---	---	---
Methocel K100M IP/BP	---	---	44.5	---	---	---	---	44.5	---	---
Ethyl cellulose 20 cps IP/BP	----	---	---	44.5		----	---	---	44.5	
HPMC 15cps IP/BP	----	---	---	---	44.5	----	---	---	---	44.5
M.C.C.P pH102 IP/BP	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5
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	30	30	30	30	30	30	30	30	30	30
Purified Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	----.	----	----	----	----
Magnesium Stearate IP/BP	4	4	4	4	4	4	4	4	4	4
TOTAL	**525 mg**	**525 mg**	**525 Mg**	**525 Mg**	**525 mg**	**525 Mg**	**525 Mg**	**525 mg**	**525 mg**	**525 mg**

III. Results:

After the evaluation of all trials, the results of physical properties are provided in Table 4, Physical Parameters of Pacritinib Citrate Sustain Release Tablets Trial Batches in Table5,
Chemical Evaluation of Pacritinib Citrate SR Tablets Trial Batches in Table 6 and Physical Parameters of Selected Pacritinib Citrate Sr Film Coated Tablets in Table 7 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
F1	0.56	0.78	6.20	0.71
F2	0.59	0.83	11.91	0.71
F3	0.46	0.76	15.47	0.60
F4	0.66	0.85	7.35	0.77
F5	0.69	0.88	9.59	0.78
F6	0.59	0.84	15.23	0.70
F7	0.75	0.92	10.47	0.81
F8	0.72	0.89	8.10	0.80
F9	0.71	0.88	7.31	0.80
F10	0.73	0.89	6.97	0.82

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

Trial	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	525 ± 2 %	3.9 ± 0.2	8-10	0.24
F2	525 ± 2 %	3.8 ± 0.2	10-11	0.26
F3	525 ± 2 %	3.6 ± 0.2	12-14	0.12
F4	524 ± 2 %	3.6 ± 0.2	10-11	0.17
F5	527 ± 2 %	3.7 ± 0.2	5-6	0.43
F6	525 ± 2 %	3.7 ± 0.2	8-10	0.24
F7	525 ± 2 %	3.6 ± 0.2	10-11	0.26
F8	525± 2 %	3.7 ± 0.2	12-14	0.15
F9	524 ± 2 %	3.7 ± 0.2	10-11	0.12
F10	527 ± 2 %	3.8 ± 0.2	5-6	0.43

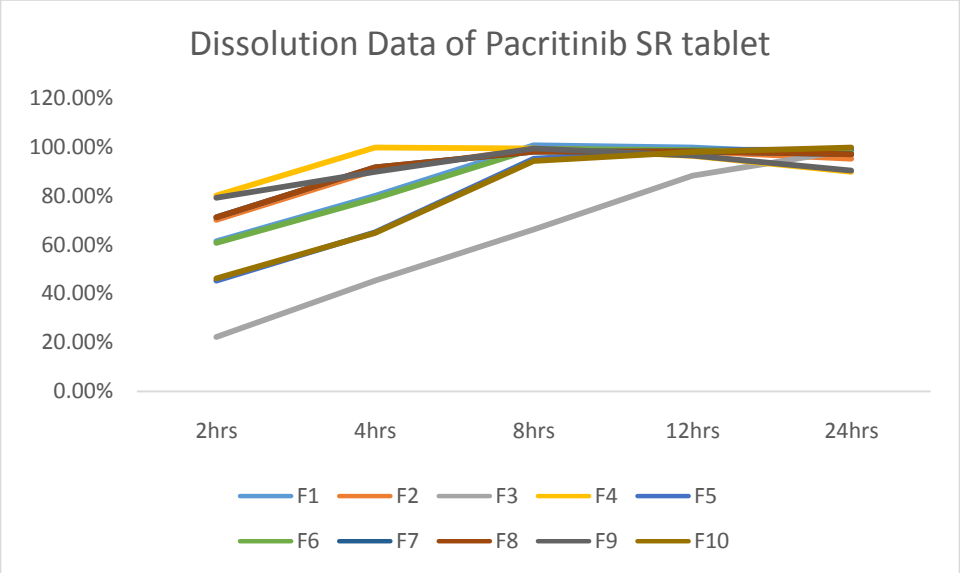
Table6: Chemical Evaluation of Pacritinib Citrate SR Tablets Trial Batches

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)
F1	101.5	61.5%	80.1%	100.9%	99.98%	96.94%
F2	99.08	70.31%	90.59%	99.35%	98.25%	95.23%
F3	99.75	22.29%	45.35%	66.34%	88.31%	98.99%
F4	99.33	80.21%	99.98%	99.65%	96.51%	90.02%
F5	99.46	45.37%	65.23%	95.37%	98.99%	99.01%
F6	100.05	60.9%	79.1%	99.47%	99.01%	97.83%
F7	100.75	71.28%	91.74%	98.26%	98.37%	97.18%
F8	99.89	71.28%	91.74%	98.26%	98.37%	97.18%
F9	101.11	79.29%	89.93%	99.51%	96.65%	90.51%
F10	102.33	46.25%	64.95%	94.36%	98.09%	99.93%

Table 7: Physical Parameters of Selected Pacritinib Citrate Sr Film Coated Tablets

Trial	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)
F7	335 ± 2 %	4.2 ± 0.2	4.5 to 5.5

Fig 1: Dissolution of all formulations



IV. Discussions:

1. The results of physicochemical evaluation of tablets are given in point no 9.5. The tablets of different batches were found uniform with respect to thickness (4.2 ± 0.2mm), diameter (12.7 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 K100M, Lactose, Maize starch,and Magnesium Stearate, colloidal silicon dioxide could be prepared satisfactorily by Wet granulation method.
3. The results of *in vitro* drug release studies in phosphate buffer pH 7.5 (from 2 to 24 h) are presented in Fig. 9.6 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 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 HPMC alone in the formulation that aids high degree of swelling.
6. Formulations of HPMC were selected for further development process because drymix of HPMC 100KM showed a rapid drug release and wet granulation shows retard HPMC K100M to give Controlled drug release. Formulations with HPMC 15K M showed a less drug release and lower than HPMC K15M also to give still lower drug release.
7. Concentration of Ethyl cellulose not controlled the release profile of Pacritinib Citrate.
8. Diluents like Lactose and Maize starch were used for reducing the rigidity of swollen matrix in addition to increase the flow ability of Pacritinib Citrate.
9. Among these tablets, the release profile of Batch no.F3 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.F2 was modified by replacing the grade of HPMC to K100M. Compared to other prepared formulations, Batch no.F3 released controlled amount of drug in the initial hours of dissolution study. The results indicated that Batch no.F3 released the drug in a manner, follow first order release kinetics. Hence Batch no.F3 can be considered as better formulation among the prepared sustained release tablets.
10. The similarity in the release profiles of marketed 2 nos tablet and formulation Batch no.F3 was compared by making use of "Model dependent approach". A simple model dependent approach used.
11. For Batch no. F3 formulation, when compared with marketed tablet, follow first order kinetics. It also show a low level of impurity that is 0.4% individual impurities and 0.6% total impurity.
12. Hence the optimized tablet Batch no.F3 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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