International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 935-940 www.ijprajournal.com ISSN: 2249-7781

Design and development of pacritinib sustained release tablet using Dry granulation technique.

Subhakanta Kanungo*, Dr. Santosh kumar Panda[1]
**PhD Scholar, Ramachandra Chandravansi University*
[1] Principal and Professor, Ramachandra Chandravansi University

Submitted: 01-04-2023 Accepted: 08-04-2023

ABSTRACT
Dry granulation technique uses to form conventional and modified release tablet from last three decades. Introduction of modified excipients boosting the preference of manufacturing using dry granulation method. Most of the moisture sensitive drugs prepared using dry granulation method. 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 by using various hydrophilic polymers like HPMC 15 CPS, HPMC K4M, HPMC K15M CR, HPMC K100M CR and Ethyl cellulose 20cps. Dry granulation was evaluated for the preparation of tablets to reduce the manufacturing time. The formulated tablets were subjected to various evaluation tests like weight variation, hardness, assay, disintegration and dissolution tests. Finally, it was concluded that the D7 batch shows the best results, amongst all formulated batches.

Keywords: Extended-release, systems, Sustained release systems, Pacritinib citrate, myelofibrosis, dry granulation

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 is 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]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 935-940 www.ijprajournal.com ISSN: 2249-7781

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
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 112	Dupont
Colloidal silicon dioxide (Aerosil)	Madhusilica
Maize Starch	Gujrat starch
Magnesium Stearate	Nikitha Pharma

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 dry granulation process with Hydrophilic polymers of different grade. The cohesiveness and compressibility of powders is improved using special grade microcrystalline cellulose 112 which support initial flow properties for slugging of powder to adhere to each other so that they can be formed into compacted 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 compacted by the dry method called dry granulation to obtain suitable flow and cohesive for compression. In this process, the proportion of the microcrystalline cellulose required adequate quantity imparting adequate compressibility and flow is much free flow than that of the dry blend needed to produce a tablet by direct mixing compression.[11-14] The various steps of formulation trials D1 to D10 are given in Table 2.

Table 2: The various steps of formulation trials D1 to D10

S.No.	Mfg Steps	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
1.	Dry sifting	√	√	√	√	√	√	√	√	√	√
2.	Dry Mixing	√	√	√	√	√	√	√	√	√	√
3.	Dry granulation	√	√	√	√	√	√	√	√	√	√
4.	milling	√	√	√	√	√	√	√	√	√	√
5.	Sieving	√	√	√	√	√	√	√	√	√	√
6.	Lubrication	√	√	√	√	√	√	√	√	√	√
7.	Compression	√	√	√	√	√	√	√	√	√	√

Formulation of batches:

The various formulations are provided in Table 3.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 935-940 www.ijprajournal.com ISSN: 2249-7781

Table 3: The various steps of formulation trials D1 to D10

Ingredients (mg)	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**
Granulation process	**Dry granulation**									
Pacritinib Citrate	400	400	400	400	400	400	**400**	400	400	400
Methocel K4M IP/BP	244.5	--	---	---	---	344.5	**--**	---	---	---
Methocel K15M IP/BP	---	244.5	---	---	---	---	**344.5**	---	---	---
Methocel K100MCR IP/BP	---	---	244.5	---	---	---	**---**	344.5	---	---
Ethyl cellulose 20 cps IP/BP	----	---	---	244.5		----	**---**	---	344.5	
HPMC 15cps IP/BP	----	---	---	---	244.5	----	**---**	---	---	344.5
M.C.C.P pH112 IP/BP	484.5	484.5	484.5	484.5	484.5	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	30	30	30	30	30	30	**30**	30	30	30
Magnesium Stearate IP/BP	4	4	4	4	4	4	**4**	4	4	4
TOTAL	**1200 mg**	**1200 mg**	**1200 Mg**	**1200 Mg**	**1200 mg**	**1200 Mg**	**1200 Mg**	**1200 Mg**	**1200 Mg**	**1200 Mg**

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 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**
D1	0.46	0.60	23.63	1.30
D2	0.47	0.63	24.52	1.32
D3	0.52	0.58	10.20	1.11
D4	0.56	0.70	20.00	1.25
D5	0.43	0.49	13.55	1.15
D6	0.52	0.55	06.25	1.06
D7	0.50	0.55	9.80	1.10
D8	0.47	0.53	11.11	1.12
D9	0.52	0.58	10.20	1.11
D10	0.60	0.72	16.66	1.20

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 935-940 www.ijprajournal.com ISSN: 2249-7781

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

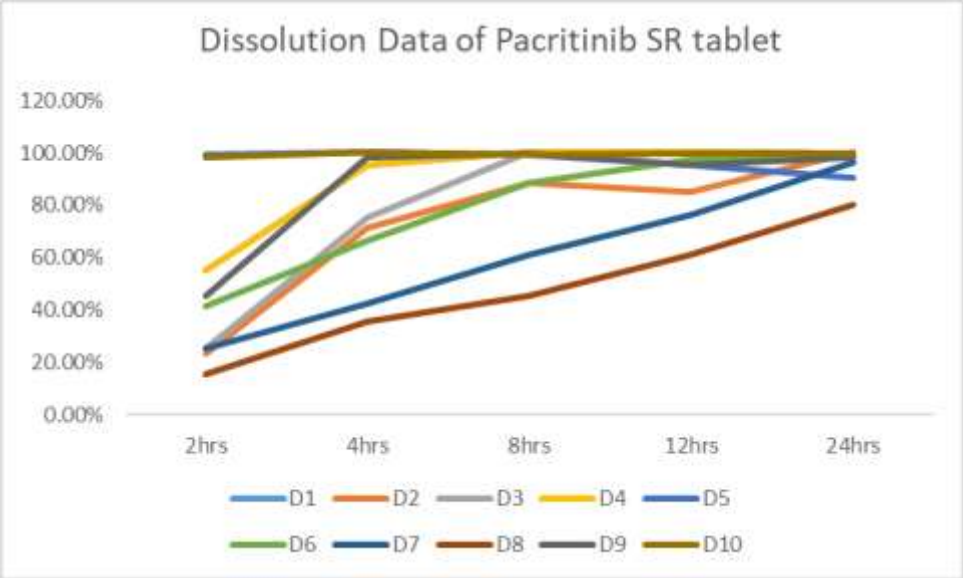
Trial	**Weight Variation (mg)**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**
D1	1200 ± 2 %	6.1 ± 0.2	10-14	0.75
D2	1200 ± 2 %	6.1 ± 0.2	11-12	0.63
D3	1200 ± 2 %	6.1 ± 0.2	10-13	0.66
D4	1200 ± 2 %	6.1 ± 0.2	10-12	0.59
D5	1200 ± 2 %	6.1 ± 0.2	8-11	0.74
D6	1200 ± 2 %	6.1 ± 0.2	9-12	0.59
D7	1200 ± 2 %	6.1 ± 0.2	9-11	0.45
D8	1200 ± 2 %	6.1 ± 0.2	9-11	0.65
D9	1200 ± 2 %	6.1 ± 0.2	10-12	0.68
D10	1200 ± 2 %	6.1 ± 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)**
D1	99.8%	55.38%	95.45%	100.32%	100.45%	99.63%
D2	100.02%	23.38%	71.45%	88.35%	85.23%	100.46%
D3	98.35%	25.38%	75.45%	100.32%	100.45%	99.63%
D4	99.10%	55.38%	95.45%	100.32%	100.45%	99.63%
D5	99.26%	99.45%	100.23%	99.32%	95.45%	90.63%
D6	100.21%	41.23%	66.35%	88.32%	97.35%	99.36%
D7	99.46%	25.36%	42.37%	61.26%	76.42%	96.45%
D8	99.78%	15.25%	35.36%	45.25%	61.26%	80.15%
D9	**99.90%**	**45.36%**	**98.25%**	**99.63%**	**95.45%**	**98.30%**
D10	**99.87%**	**98.38%**	**100.32%**	**99.36%**	**99.56%**	**99.56%**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 935-940 www.ijprajournal.com ISSN: 2249-7781

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 (6.1 ± 0.2mm), diameter (12.5 X 8 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, Lactose, Maize starch, and Magnesium Stearate, colloidal silicon dioxide could be prepared satisfactorily by dry 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. 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 one after one basis.
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 of HPMC K4 MCR grade showed slow drug release if present in higher concentration. Formulations with HPMC 15K MCR showed a sustained drug release compare to HPMC K100MCR in a higher concentration. Formulation D8 prepared using HPMC K100 M CR unable to deliver 100% drug in 24 hour compared to formulation D7 which release 100% drug in 24 hours.
7. Concentration of Ethyl cellulose not controlled the release profile of Pacritinib Citrate in dry granulation method formulation and process need to optimized with high concentration of ethyl cellulose and coating using spray drying method.
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. D7 was found to be nearly matching to that of the 2 nos of marketed tablet. Cumulative release drug comparatively controlled from the initial interval. In the further development process, formulation Batch no. D6 was modified by replacing the grade of HPMC K4M to K15MCR. Compared to other prepared formulations, Batch no. D7 released controlled amount of drug in the initial hours to end hours of dissolution study. The results indicated that Batch no. D7

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 935-940 www.ijprajournal.com ISSN: 2249-7781

released the drug in a manner, follow first order release kinetics. Hence Batch no. D7 can be considered as better formulation among the prepared sustained release tablets.

10. The similarity in the release profiles of marketed 2 no's tablet and formulation Batch no. D7 was compared by making use of "Model dependent approach". A simple model dependent approach used.
11. For Batch no. D7 formulation, when compared with marketed tablet, follow first order kinetics. It also shows a low level of impurity that is 0.2% individual impurities and 0.1% total impurity.
12. Hence the optimized tablet Batch no. D7 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.

Acknowledgement
The authors would sincerely like to thank BOC Sciences, Colorcon, Degussa, Dupont, Madhusilica, Gujrat starch, Nikitha Pharma and Indian Glycol for supplying API and excipients'.

REFERENCES

[1]. Vyas SP, Khar RK, Controlled drug delivery: concepts and advances, 1st edition, Vallabh prakashan, New Delhi, 2002.
[2]. Chein YW, Novel Drug Delivery System, 2nd edition, Marcel DekkerInc; New York, 1992, p.2.
[3]. Verma RK, Garg S, Current status of drug delivery technologies and future directions, Pharma Techno., 2001; 25(2), p.1-13.
[4]. Alfonsa, R.Gennaro, Remington's Pharmaceutical Sciences, 18th edition, 1990, p.1677-1678.
[5]. A S Hussain, Vinob P. Shah 'The Biopharmaceutical Classification System: Highlights of the FDA's draft Guidance' Office of pharmaceutical sciences, CDER, FDA, Rockville MD.
[6]. Randall CS. 'Physical Characterization of Pharmaceutical Solids' Marcel Dekker Inc New York, 1995, 180 – 182.
[7]. United States Pharmacopoeia-30: National Formulary-25 , Vol .1, Asian edition, United States Pharmacopoeial Convention, Inc; 2007, p.242, 318, 644, 645, 832.
[8]. www.accessdata.fda.gov/scripts/cder/iig/getiig WEB.cfm
[9]. Brown Cynthia K. Chokghittitesh P., Nickerson Beverby, Reed Robert A., Rohrs Brian R., and Shah Pankaj A, Acceptable Analytical practices for Dissolution testing of poorly soluble compounds. **Pharmaceutical Technology** December 2004, 60.
[10]. Food and drugs Administration, Guidance for industry, Dissolution testing of immediate release solid and dosage forms.
[11]. Amidon G.L., Lennernas H., Shah V.P., and Crison J.R., "A theoretical basis for a Biopharm of in-vitro drug product dissolution and in vivo bioavailability" Pharmaceutical research 12, 413-420.
[12]. Ford, J.L., Rubibstein, M. H. and Hogan, J.E., Formulation of Sustained Release Promethazine hydrochloride Tablets using Hydroxy propyl methyl cellulose matrices.Int. J. Pharm., 24,327-338(1985)
[13]. Mahaguna, V., Talbert, R. L., Peters, J. i. Adams, S., Reynolds. D., and Lam, F. Y. W., Influence of Hydroxy methyl cellulose polymer on in vitro & in vivo performance of controlled release tablets containing Alprozolam Eur.j.pharm.biopharm., 56,461-468. (2003).
[14]. Nellor,R. V.,Rekhi, G. S.,Hussein, A.S.,Tilman,L.G.,and Augsburg, L.L.,Development of Metroprolol tartrate extended -release matrix tablet formulation for regulatory policy consideration.J.Controlled.Rel.,50,247-256,(1998).