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Formulation and evaluation of apixaban tablet

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Abstract:-

The oral drug delivery system which includes the solid dosages form such as conventional dosages form and immediate release dosages form. Tablet is most popular among the all dosages forms today and recently found mostly accepted tablet dosages forms. Because of its convenience easy to administration, convenience of self-administration, compactness and easy for the manufacturing. In number of cases immediate onset of action is required than conventional therapy. The basic approach used in development immediate release solid dosages form by using superdisintegrant like sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone (PVP) etc. which provides in instantaneous disintegration of tablet after administration. By using various techniques in can be formulate like wet granulation, direct compression etc. Hence its having a new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. Prepared batches were evaluated for all pre-compression parameters and post-compression parameters.

Keywords: Apixaban, CCS, Direct compression method

Introduction

Apixaban (fig. 1) [1] is chemically 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl) phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo [3,4-c] pyridine-3-carboxamide. It is a new generation of oral anticoagulant drug that selectively inhibits coagulation factor Xa [1]. It is used in thromboprophylaxis in patients following total knee replacement surgery with a desired efficacy and safety profile [2]. FDA approved apixaban (Eliquis, Bristol-Myers Squibb/Pfizer) on December 28, 2012, for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) [3]. Apixaban is not an official drug in any Pharmacopoeia. Literature survey reveals that only one marketed formulation of apixaban is available which is very costly and cannot afford to poor patients. Therefore, a cost-effective formulation as compared to the marketed formulation is developed. Some methods have been reported for their determination of apixaban by HPLC [4] and hyphenated

techniques such as UPLC– MS/MS [5], LCMS [6], GCMS [7], either alone or in combination. This paper presents formulation development of apixaban as well as development and validation of stability indicating assay method by using the RP-HPLC technique.

The common analgesic drug Apixaban shows bad dissolution and tableting behavior due to its hydrophobic structure. Additionally its high cohesivity results in low flowability. Another problem in its manufacturing is its high tendency of sticking to the punches. There are three methods of tablet manufacturing with the choice depending upon the dose and the drug's physical properties, such as, compressibility and flow of the blend. Direct compression is a process by which tablets are compressed directly from mixtures of the drug and excipients, without any preliminary treatment. A simple formula is considered to be composed of an active ingredient, a diluent and a lubricant.

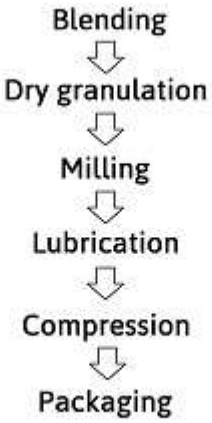


Fig.1 Direct compression process

Techniques in direct compression [11]

The processes involved in the manufacture of tablets by direct compression method can be summarized in three steps.

1. Direct compression technique using induced die feeders

2. Direct compression technique using dry binders and

3. Direct compression technique using direct compression excipients

Direct compression technique using induced die feeders

Direct compression technique using induced die feeder is used when formulation ingredients will compact but will not adequately fill the die cavity.

Advantages of direct compression technology

The adoption of direct compression technology is based on the following advantages or benefits

1. Direct compression method requires fewer processing steps (unit operations) and less equipment. Therefore, the method is potentially less expensive than other methods used in tablet manufacture.

2. Tablet manufacture can be carried out without the involvement of moisture and heat. Hence, product stability is almost guaranteed.

3. Some direct compressible excipients possess inherent disintegration properties e.g., microcrystalline cellulose.

4. Tablets produced by direct compression method generally show faster dissolution times than those prepared by wet granulation. This is because tablets manufactured by direct compression method disintegrate into primary particle state unlike those manufactured by wet granulation method which breaks down into granules and finally into primary particle state.

5. Changes in dissolution profile are less likely to occur in tablets manufactured by direct compression (if stored for a long time) than in those prepared by wet granulation.

6. Because direct compression excipients have a relatively high binding capacity, the pressure required to manufacture the desired hardness is, in general, less with direct compression vehicles than with conventional granulations, resulting in both higher production rates and longer machine life.

7. Lubrication is performed in the same vessel as powder mixing, thereby reducing both transfer losses and contamination of equipment.

Materials and Methods

Materials

Commercially available tablets of apixaban (5 mg) were procured from local market and apixaban API was obtained from an approved supplier. All excipients were obtained from Active Fine Chemical Ltd., Dhaka, Bangladesh. HPLC grade solvents used in this study were obtained from Active Fine Chemical Ltd., Dhaka, Bangladesh.

Instruments

Apixaban tablets were formulated on single punch tablet compression machine Mini press 1 (Karnavati Engineering limited). The friability test was performed on Electrolab EF-2 friabilator USP. Disintegration test was performed on Electrolab disintegration tester ED-2L. The dissolution testing was performed on Labindia DS 8000. The method was performed on Shimadzu LC 2010 CHT, Japan having a quaternary system with automatic injection facility and UVVisible detection system. The column used was Purospher Star RP-18e (5 µm, 250x4, 6 mm), LC solution software and Shimadzu AY-120 balance was used for this work.

Formulation of tablets

Before formulation and pre-formulation studies (organoleptic properties, solubility, and drug excipient compatibility studies) were carried out. Apixaban tablets were formulated by using 32factorial design as presented in table 1. Drug, binder, super-disintegrant and other excipients were weighed separately for 60

tablets per batch as per proposed formulations. The proposed formulations were coded as F1, F2, F3, F4, F5, F6, and F7. The amounts of drug and excipients are expressed in mg (milligram) unit. Initially, the binder, super-disintegrant and other excipients were passed through sieve no. 40. Then, apixaban (API) was added, mixed properly for 5-10 min and sieved again. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (100 mg). Tablets were prepared using flat face round 6.5 mm diameter punch by the direct compression process.

Table-1 Formulation methods

Ingredient(mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Apixaban	5	5	5	5	5	5	5
Lactose	49	54	44	54	46	45	44
MCC	30	30	30	30	30	30	30
CCS	3	3	5	5	5	7	7
Mag stearate	2	2	2	2	2	2	2

Evaluation of tablets

Appearance

Take about 20 tablets in a watch glass and observe visually with white to off white background check the color, shape and size.

Identification

The chromatogram of the sample preparation exhibits a major peak for Apixaban, the Retention time of which corresponds to that exhibited in the chromatogram of the standard

Preparation as obtained in the assay.

Average Weight:

Weigh 20 tablets individually at random basis and record the weight.

Hardness, Thickness & Diameter

Take 10 tablet and measure Hardness (in kp), Thickness (in mm) & Diameter (in mm) with LABINDA test tablet tester. Take average value of Hardness (in kp), Thickness (in mm) & Diameter (in mm) as result.

Friability

Take 20 tablets; remove any loose dust with soft brush. Weigh the tablets (W1) and place the tablets in the drum of Friability Tester Put the tablet in Friability Tester. Run the instrument at 25 RPM for 4 minutes and remove any loose dust from the tablets as before. If no tablet cracked, split or broken, weigh the tablets (W2).

Result and discussion:

The present study of apixaban immediate release tablets were developed with a view to deliver the drug immediately. The formulation development work was initiated with wet granulation method and a total of 7 formulations were made. The formulated tablets were evaluated for various pre compression parameters and post compression parameters like thickness, hardness, weight variation, friability, disintegration test, drug content uniformity and in vitro release studies. The formulation F7 showed satisfactory physical parameters, and it was found to be stable among other formulations.

Table-2- The flow characterization

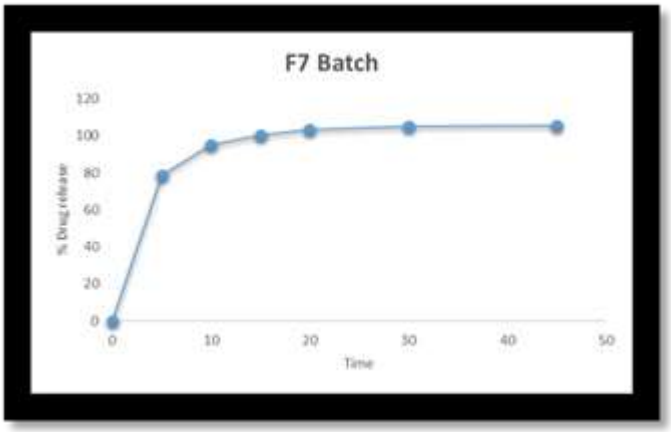
Batch	Bulk density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hauser's ratio
F1	0.606	0.689	12.04	1.13
F2	0.571	0.714	12.02	1.25
F3	0.588	0.666	11.71	1.13
F4	0.606	0.714	15.12	1.17
F5	0.588	0.689	14.65	1.17
F6	0.588	0.714	17.64	1.21
F7	0.577	0.750	23.077	1.30

Table-3-Evaluation parameters of tablets

Batch	Thickness	Hardness	Friability (%)	Disintegration time
F1	3.70±0.2	130-140N	0.07%	6 – 8 min
F2	3.70±0.2	130-140N	0.06%	2 – 3 min
F3	3.70±0.2	150-170N	0.01%	6 – 8 min
F4	3.70±0.2	150-170N	0.02%	3 – 5 min
F5	3.70±0.2	150-160N	0.03%	4 – 6 min
F6	3.70±0.2	150-160N	0.02%	4 – 6 min
F7	3.70±0.2	150-160N	0.02%	4:30 – 5 min

In-vitro release profile of F7 batch

S. No.	Time (min)	%Drug release
1	5	78.5
2	10	95.2
3	15	100.4
4	20	103.5
5	30	104.9
6	45	105.5



Conclusion:

Batch F7 was determined to be a promising formulation appropriate for the immediate release of apixaban based on the formulation evaluation. The stability of the assay method's results indicates its simplicity, accuracy, specificity, sensitivity, and precision.

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