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FORMULATION AND EVALUATION OF EFFERVESCENT TABLETS OF IMATINIB MESYLATE

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ABSTRACT

A pill was originally defined as a small, round, solid pharmaceutical oral dosage form of medication. Today, pills include tablets, capsules, and variants thereof like caplets — essentially, any solid form of medication colloquially falls into the pill category.An early example of "pills" came from Ancient Rome. They were made of the zinc carbonates hydrozincite and smithsonite. The pills were used for sore eyes, and were found aboard a Roman ship.Relitto Del Pozzino which wrecked in 140 BC. However, these tablets were meant to be pressed on the eyes, not swallowed. A caplet is a smooth, coated, oval-shaped medicinal tablet in the general shape of a capsule. Many caplets have an indentation running down the middle so they may be split in half more easily. Since their inception, capsules have been viewed by consumers as the most efficient method of taking medication. For this reason, producers of drugs such as OTC analgesics wanting to emphasize the strength of their product developed the "caplet", a portmanteau of "capsule-shaped tablet", in order to tie this positive association to more efficiently-produced tablet pills, as well as being an easier-to-swallow shape than the usual disk-shaped tablet.

KEY WORDS: Hydrazones, Arachidonic Acid, Nabumetone, Naproxen, Prostaglandins.

INTRODUCTION

Effervescent tablets are also known as carbon tablets which has capable of releasing co2.Effervescent tablets are formulated by mixing these agents citric acid, sodium bicarbonate, tartaric acid along with binders, diluents and lubricants, and then compressing them into tablets [1]. The rate of effervescent can be modified with the use of plasticizer. Basically, increasing the amount of plasticizer prolongs the rate of effervescence. Increasing hydrophobic binder amount reduces the rate of effervescence. Effervescence granules are manufactured in low humidity areas [2]. Effervescent tablets can be coated to have drug release at desired site in GIT. There are several methods for the preparation of effervescent tablets but the prepared products vary in their properties depending on the method of preparation. The property in which they vary are hardness, friability, effervescent time, pH content uniformity. The most widely used process of agglomeration in pharmaceutical industry is wet granulation [3]. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

Dug Profile

Molecular formula: C29H31N7O
Synonyms: Imatinib
Molecular weight: 589.7g/m01
Appearence Imatinib mesylate is a white and amorphous in nature

Drug bank code

Pka : DB00619
Brand name: Gleevec, Gleevec
Bio availability: 97-98%
Iupac name: 4-(4-methylpiperazin-1yl) methyl)-N-(4-methyl-3-{[4-(pyridine-3yl) pyrimidin-2-yl] amino} phenyl) benzamide
Melting point: 211-213 C

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METHODOLOGY

Granulation Process

Methods which can be used for preparation of effervescent granules are as follows-

a) Wet granulation

Wet granulation is still the most preferred method for effervescent granulation. This method gives homogeneous granules for compression, and is able to provide uniform tablets either in terms of weight or active ingredient content. Wet granulation method further can be divided in two types depending on the number of process steps. We are using one step process and it is as follows [4].

Precompression Parameters

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first development in the rationale development of the dosage forms [5]. Pre-formulation studies yields necessary knowledge to develop suitable formulation for toxicological use. It gives information needed to define the nature of the drug substance and provide a dosage form. Hence, the following pre-formulation studies were performed for the obtained sample of drug [6].

Bulk density

Bulk density of a compound various substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre-sieved granules into a graduated cylinder via a large funnel and measure the volume and weight [7].

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

Bulk density was expressed in g/cc.

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed [8].

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Trapped volume of granules}}$$

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density/Bulk density

Carr's Index (CI): Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$Cl = \frac{(TD-BD)\ x100}{}$$

Where,

TD = Tapped density BD = Bulk density

Angle of repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal.[9]

Tano = h/r

Where, h= height of the heap r= Radius of the heap

Post Compression Parameters

Evaluation of Tablet

A. Physical Evaluation of tablets

Weight Variation: - it was performed as per the method given in the Indian pharmacopoeia. Tablets were randomly checked to ensure the proper weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.[10]

Ten tablets were taken randomly and weighed accurately. The average weight was calculated by,

$$\text{Average weight} = \frac{\text{weight of 10 tablets}}{10}$$

Hardness test

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture. The tablet hardness of 7Kp is considered as suitable for handing the tablet [11].

Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Callipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition, thickness must be controlled to facilitate packaging [12].

Dimensions

The thickness and diameter of the tablets was determined using a micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated.

Friability

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these

are placed in the Roche friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0% [13]

%Friabi1ity = (WI-W2)/W1 X 100

Where,

W 1= weight of tablets before test

W2 = weight of tablets after test

Effervescence Time

Measurement of effervescence time A single tablet is placed in a beaker containing 200 ml of purified water at 20 °C ± 1 °C. Whenever a clear solution without particles is obtained effervescence time has finished. The mean of three measurements of each formulation is to be reported.[14]

pH of Effervescence Solution

Determination of effervescent solution pH pH of solution is determined with one tablet in 200 ml of purified water at 20 ± 1 °C by using pH meter, immediately after completing the dissolution time. Repeat experiment 3times for each formulation.

Measurement of CO2 Content

Measurement of CO2 content one effervescent tablet solved in 100 ml of 1N sulphuric acid solution and weight changes were determined after dissolution end. The obtained weight difference is shown the amount (mg) of CO2 per tablet. Reports the averages of 3 determinations. [15]

Evaluation of Water Content

Evaluation of the water content 10 tablets of each formulation are dried in a desiccator containing of activated silica gel for 4 hours. Water content of 0.5% or less is acceptable.

Uniformity of Content

10 tablets were selected randomly. Each tablet was transferred into a 50 ml volumetric flask, dissolved and diluted to 50 ml with phosphate buffer PH 6.8. One ml of the solution was diluted to 100 ml with phosphate buffer PH 6.8. The amount of drug present in each tablet was determined by UV spectroscopy at 246nm. Standard limit for uniformity of content is [17]

IP: Active less than 10mg or 10%.

BP: Active less than 2mg or 2%.

USP: Active less than 25mg or 25%

10 tablets limit NMT 1 tab deviate 85-115% and none outside 75-125% of the average value/IP/BP/USP (Relative standard deviation less than or equal to 6%)

If 2 or 3 individual values are outside the limits 85-115% of the average value and none outside 75-125% repeat for 20 tablets.

Invitro Disintegration Test

The in-vitro disintegration time was determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds. I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at $37^0 \pm 2^0$c as the immersion liquid. The assembly should be raised and; lowered between 30 cycles per minute in the PH 6.8 maintained at 37 $^0 \pm 2^0$c.the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Ratios of methyl cellulose (MC), sodium carboxymethylcellulose (CMC) and hydroxypropyl-methylcellulose (HPMC). Each of the formulations contain methyl paraben 0.2%, potassium chloride 0.062%, magnesium chloride 0.005%, potassium phosphate 0.034%, sodium fluoride 0.01%, dextrose 4.69% and flavour.[17]

***Invitro* Dissolution Study**

Following parameters were used for the dissolution study

1: Apparatus: Dissolution apparatus

2: Speed of the paddle: 50rpm

3: Temperature: 37 c+_0.5c

4: Dissolution Medium: Phosphate buffer, ph:6.8

5: Volume of fluid: 900ml

6: Sample size: USP dissolution apparatus Type2 (paddle type)

Samples of 10 ml, was withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analysed spectrophotometrically at 281 nm.

RESULTS AND DISCUSSION

Characterization of imatinib mesylate

1. Physical properties
2. Spectrophotometric characterisation
3. Evaluation of powder blender (pre compression) Evaluation of tablet(post compression studies) conclusion
4. Physical Properties: -
5. Colour, Appearance: - White or pale yellowish, crystalline powder.
6. Melting Point determination: - Melting point of imatinib mesylate was found in the range between 211 ^{0} C-213.4^{0}C. The reported melting point range of imatinib mesylate was found to be 212.4 C

C. The experimental values similar with official value.

1. Solubility: - soluble in water.
2. Spectrophotometric Characterization: -

1. Calibration curve of imatinib mesylate:

Absorbance verses drug concentration was plotted to construct a standard curve for imatinib mesylate. The poly nominal regression for the calibration plots showed good linear relationship in water. P.H 7 medium over the concentration range studied [18].

Blend Properties of imatinib mesylate prepared by wet granulation Technique.

Precompression characteristics of imatinib mesylate tablet. Hence flow properties viz., angle of repose, bulk density, tapped density and hausner's ratio were determined and given in Table 5. Bulk density, was found in the range of 0.42-0.46g/cm3 and the tapped density between 0.5 and 0.57 g/cm3 and hausner's ratio was in the range of 1.13-1.35. The Carr's index was found ranged from 13.6 to 26.66. This indicates a fairly good flowability of the powder blend. The good flow ability of the powder blend was also indicated by the angle of repose, which is in the range of 21.84 -27.82 which is below 30 indicating good flowability.[19]

Hardness test

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data. The results showed that the hardness of the tablets is in range of 2.5 to 3.5 kg/cm2, which was within IP limits [20].

Thickness

Thickness of three tablets of each batch was checked by using Vernier Callipers and data shown in Table. The result showed that thickness of the tablet is raging from 5.3 -5.8 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data are shown in the Table 4. The average friability of all the formulations lies in the range of 0.6 to 0.95% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Weight Variation

Weight variation was performed and the data are shown in the Table 6. The weight variation was less than 5% deviation and satisfied as per official requirement of IP.

In vitro disintegration time

Tablets of each batch were evaluated for in vitro disintegration time and the data's were shown in the Table 7. The results showed that the disintegration time of prepared tablets were in the range of 29 to 68 seconds.

Uniformity of Content

10 tablets were selected randomly. Each tablet was transferred into a 50 ml volumetric flask, dissolved and diluted to 50 ml with phosphate buffer PH 6.8. One ml of the solution was diluted to 100 ml with phosphate buffer PH 6.8. The amount of drug present in each tablet was determined by UV spectroscopy at 246nm. Standard limit for uniformity of content is

IP: Active less than 10mg or 10%.

BP: Active less than 2mg or 2%.

USP: Active less than 25mg or 25%

10 tablets limit NMT 1 tab deviate 85-115% and none outside 75-125% of the average value/IP/BP/USP (Relative standard deviation less than or equal to 6%). If 2 or 3 individual values are outside the limits 85-115% of the average value and none outside 75-125% repeat for 20 tablets [21].

Table 1. Formulation of effervescent tablets of imatinib mesyalte formulation of tablet

INGEREDIENTS (mg)	F1	F2	F3	F4	F5	F6
Imatinib mesylate	100	100	100	100	100	100
Citric acid	150	100	150	150	175	200
Sodium bicarbonate	50	100	75	100	100	140
Tartaric acid	0	50	75	75	75	50
Saccharin	5	5	5	5	5	5
Magnesium Stearate	2.25	2.25	2.25	2.25	2.25	2.25
Talc	2.25	2.25	2.25	2.25	2.25	2.25
Lactose	190	140	90	90	40	0
PVP	0.5%	1%	2%	3%	4%	4%
Total	500	500	500	500	500	500

Table 2. Specifications for tablets as per Indian pharmacopeia

S. N0	Average weight of tablet	% Deviation
1.	80 mg or less	10
2.	More than 80 mg but less than 250 mg	7.5
3.	250 mg or more	5

Table 3. Calibration curve of Imatinib mesylate:

Concentration(µg/ml)	**Absorbance(nm)**
0	0
2	0.1082
4	0.1103
6	0.1773
8	0.1914
10	0.2802
	0.024537143

Table 4. Parameters

Parameter/ Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (0)	Hausner's Ratio	Carr's Index (%)
F1	0.45	0.53	21.41	1.17	17.7
F2	0.44	0.53	25.67	1.13	13.6
F3	0.46	0.53	23.64	1.15	15.121
F4	0.42	0.57	27.82	1.35	35.71
F5	0.45	0.57	28.48	1.35	26.66
F6	0.44	0.53	22.42	1.13	20.45

Evaluation of Tablets

Table 5. Physical evaluation of tablets prepared by direct compression method

Formulation	Thickness (mm)	Hardness (kg/cm2)	%Friability	Weight variation(mg)
F1	5.6	2.5	0.60	502
F2	5.3	3.0	0.80	501
F3	5.4	2.8	0.77	500
F4	5.8	3.4	0.65	499
F5	5.7	2.7	0.95	498
F6	5.5	3.5	0.78	499

Table 6. Post compression parameters of tablets

Formulation	Disintegration time(min)	Effervescent time(min)	Ph of effervescent solution	Water content (%)	CO2 content
F1	5.36	7.10	7	0.54	0.23
F2	4.52	6.45	6	0.68	0.34
F3	3.56	5.45	7	0.62	0.39
F4	3.12	5.20	7	0.57	0.45
F5	2.46	3.35	7	0.52	0.52
F6	2.13	3.15	7	0.49	0.69

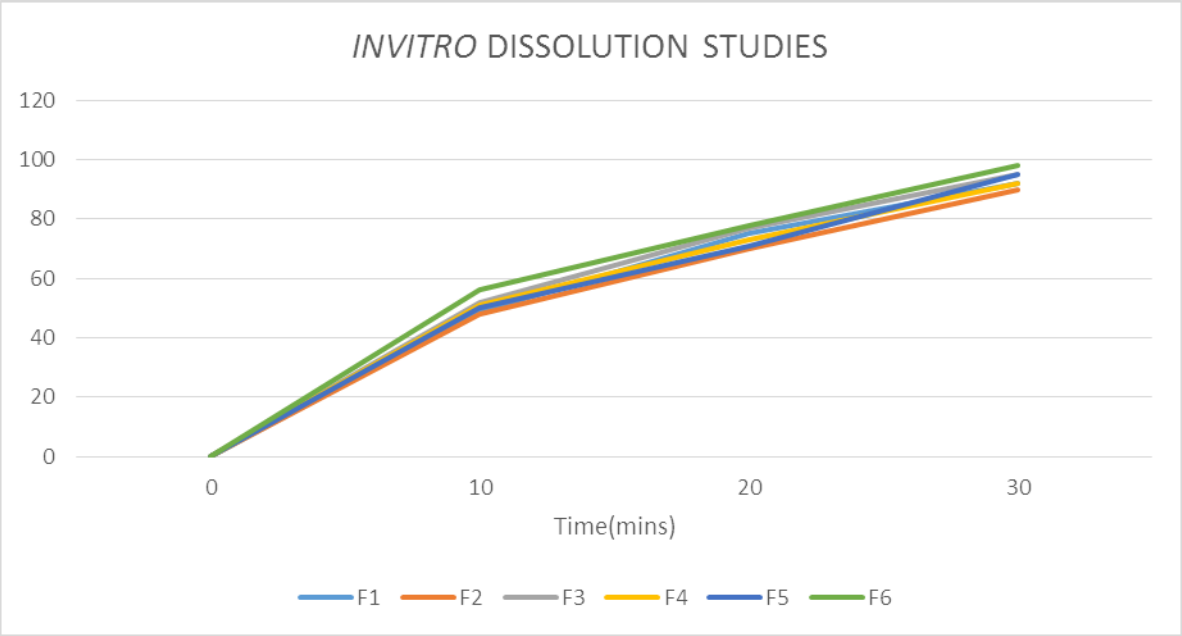
Table 7. Uniformity of Content

Formulation	Uniformity of content
F1	93.34
F2	94.12
F3	95.56
F4	96.12
F5	96.54
F6	98.75

Table 8. Invitro dissolution studies of imatinib mesylate for formulations f1- f6:

TIME (mins)		%Drug Release FORMULATION				
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	49	48	52	51	51	56

20	75	70	77	73	71	78
30	92	90	95	92	95	98



***Invitro* Dissolution studies**

Invitro dissolution studies were carried out by using 900ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min. The dissolution data for all the formulations are given in the Table.[22].

CONCLUSION

In the present work, an attempt has been made to develop effervescent tablets of Imatinib mesylate. In the present work citric acid, tartaric acid and sodium bicarbonate were employed as effervescent producing agents to produce effervescence. All the formulations were prepared by wet granulation method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F6 formulation showed maximum % drug release i.e., 98 % up to 30 min hence it is considered as optimized formulation.

SUMMARY

The present study was undertaken with an aim to formulate and evaluate effervescent tablets of Imatinib mesylate using wet granulation method with the addition of effervescent producing agents. To produce effervescent tablets of Imatinib mesylate citric acid, tartaric acid, sodium bicarbonate is used as effervescent producing agents. Flow properties viz., angle of repose, bulk density, tapped density and Hausner's ratio were determined and given in Table 5. Bulk density was found in the range of 0.42-0.45g/cm3 and the tapped density between 0.53 and 0.57 g/cm3 and hausner's ratio was in the range of 1.13-1.35. The Carr's index was found ranged from 13.6 to 35.71. This indicates a fairly good flowability of the powder blend. The resulted tablets were evaluated for their hardness, weight variation, thickness, friability, disintegration, dissolution etc.The results showed that the disintegration time of prepared tablets were in the range of 29 to 68 seconds. The effervescence time of the formulations are found to be in the range of 3.15-7.10 minutes. The tablet formulation (F6) exhibited higher dissolution rate (98% release after 30 min) as compared to that of batch containing other formulations. Thus, F6 batch was selected as promising formulation because of higher drug release, fastest disintegration time and having least effervescence time.

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Nil

CONFLICT OF INTEREST

No Interest

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