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FORMULATION AND EVALUATION OF TABLETS CONTAINING POORLY WATER SOLUBLE DRUG BY MADG METHOD.

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ABSTRACT

Tablet is a unit solid dosage form containing active ingredient with or without suitable excipient. These are most widely used dosage form.[1] The main objective of the design and manufacture of the compressed tablet is to deliver orally correct amount of drug in the proper form over proper time and at desired location, so as to have suitable chemical integrity protected at the point of its action. The physical design, manufacturing process, and complete chemical makeup of the tablet can have a profound effect on the efficiency of the drug being administered.[2] Poorly water soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability[3] and nearly 40% of the new chemical entities currently being discovered are poorly water-soluble drugs.[4] Based upon their permeability characteristics, the biopharmaceutics classification system (BCS) classifies such drugs in two major classes, i.e., Class II and IV. The BCS class II drugs are poorly water-soluble entities with high permeability. Most formulation strategies for such drugs are targeted at enhancing their fine dispersion at absorption level.[5] Ibuprofen being poorly water-soluble drug known to demonstrate dissolution or solubility limited absorption. The bioavailability of the drug is low, yet its rate of absorption is quite inconsistent and delayed with time. Based upon its aqueous solubility and various dissolution parameters, the drug bioavailability can unambiguously be regarded as limited solely to dissolution.[6] The main focus on moisture activated dry granulation method is better than other granulation method in case of poorly soluble drug tablets.

KEYWORD: *MADG, Tablets, Ibuprofen.*

INTRODUCTION

Tablet manufacturing process can be broadly classified as granulation and direct compression. Granulation process may be defined as the size enlargement process in which fine or coarse particles is converted into physically stronger and larger agglomerates having good flow properties, better compression characteristics and uniformity and a process for collecting particles together by creating bonds between them. It is the most widely used technique in the pharmaceutical industry for the preparation of materials for tableting. Granulation may be either wet granulation or dry granulation i.e., by using binder solution or, by using dry binder. Pharmaceutical granules typically have a size range between 0.2 to 4.0 mm, depending on their subsequent use. Most of formulation in tablet manufacturing is by wet granulation process.[7] **Granulation** is the process in which primary powder particles are made to adhere to form larger, multi particle aggregates called granules**.**Granulation method can be broadly classified into two types[4,5,6,7]

DRY GRANULATION		WET GRANULATION	MOISTURE ACTIVATED DRY GRANULATION
Dispensing and Shifting		Dispensing and Shifting	Dispensing and Shifting
Dry mixing		Dry mixing	Dry mixing
Slugging	~~Slugging~~	Granulation	Granulation
Half lubrication	Lubrication	Pre-drying	~~Pre-drying~~
Compression	Compression	Shifting	~~Shifting~~
Milling		Drying	~~Drying~~
Shifting		Pre-mixing (unlubrication)	Pre-mixing (unlubrication)
Final lubrication		Lubrication	Lubrication
compression		Compression	Compression

Moisture Activated Dry Granulation (MADG) was developed in response to the difficulties experienced with wet granulation, in terms of endpoint, drying and milling. Wet granulation process endpoint is very sensitive to granulation time and shear. The wet granules need to be dried to a narrow range of moisture contents, which is difficult. The dried granules need to be milled, but the milled granules often have either too many fines or too many coarse particles (or both) — an undesirable bimodal distribution.

MADG is a very simple and innovative process where granules are created with water and a granulating binder, as in wet granulation, but are not heat dried or milled. This process helps to minimize end point sensitivity.

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It is applicable to many of the pharmaceutical industry's granulation needs for solid dosage form development and can be described as a 'one-pot' granulation process.

MATERIAL AND METHOD

Ibuprofen BP was procured as a gift sample from ZIM Laboratories Ltd, Nagpur, Maharashtra. Colloidal anhydrous silicon (Aerosil) was procured as a gift sample from ZIM Laboratories Ltd, Nagpur, Maharashtra.Maize starch was procured from ZIM Laboratories Ltd, Nagpur, Maharashtra. Lactose DC was procured from ZIM Laboratories Ltd, Nagpur. PVP K30 (Povidone) was procured from ZIM Laboratories Ltd, Nagpur, Maharashtra. Microcrystalline cellulose was procured from ZIM Laboratories Ltd, Nagpur, Maharashtra. Talcum was procured from ZIM Laboratories Ltd, Nagpur, Maharashtra. All other chemicals used were of analytical grade.

Formulation and development

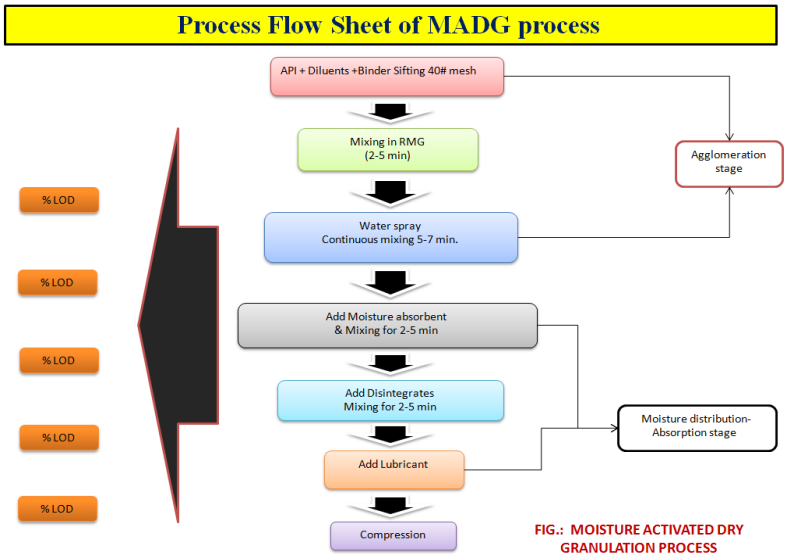
MADG is a process in which moisture is used to activate granule formation, without the need to apply heat to dry the granules. There are two main stages in MADG:

1. Agglomeration 2. Moisture distribution/ Absorption

During agglomeration, drug is mix with fillers and binder in the powder form, to obtain a uniform mixture. This blend constitutes approximately 50-80% of formula weight. While mixing, a small amount of water (0.5-5%) is sprayed as small droplets onto the powder blend, which moistens the binder and makes it tacky. The binder facilitates the binding of the drug and excipients as they move in a circular motion forced by the mixer blades. The process does not results in larger lumps formation as the amount of water used in this process is very small as compared to the other conventional wet granulation techniques. The particle size of the agglomerates generally falls in the range of 150-500 μm.

In moisture distribution/absorption, moisture absorbents, such as microcrystalline cellulose or silicon dioxide, are added while mixing continues. When they come into contact, the moisture absorbents pick up moisture from the moist agglomerates, resulting in moisture redistribution within the mixture. When this happens, the entire mixture becomes relatively dry. While

some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact and some usually the larger particles may break up. This process results in granulation with more uniform particle size distribution.[34]



Flow chart: Method for preparation of Ibuprofen tablet 400mg

Evaluation of Ibuprofen tablets

The Ibuprofen tablets were evaluated for following parameters;

1) Appearance
2) Friability
3)Weight variation
4)Disintegration time
5) Drug release study (*in-vitro*)
6) Dimensions
7) Hardness
8) Drug content
9) DSC
10) X-ray diffraction (XRD)
11) Scanning electron microscopy
12)Stability testing

Preformulation study

Flow characterization A. Bulk density

Bulk density = weight of sample in gram / volume occupied by the sample

B. Tapped density

Tapped density = Wt. of sample in g / Tapped volume

C. Hausner's ratio and Compressibility index

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast and popular methods for predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.[54]

i. Hausner's ratio

$$\text{Hausner ration} = \text{Tapped density (gm/cm}^2\text{)/ bulk density (gm/cm}^3\text{)}$$

ii. Compressibility index

$$\text{Carr's index (\%)} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \times 100$$

Table 6.8: Limits of Compressibility index and Hausner ratio

a. Angle of repose

$$\text{Tan } \theta = h/r$$

Where,

h = Height of pile, r = Radius of the base of pile, θ = Angle of repose

Table 6.9: Flow properties and corresponding angles of repose

Table 6.10: Formulation flow characterization

FORMULATION	MOISTURE (%)	BD (g/cm^3)	TD (g/cm^3)	HR	CI (%)	FLOEABILITY	Angle of repose
I01	2	0.576	0.703	1.22	19.34	Fair	36
I02	2	0.586	0.727	1.24	19.34	Fair	37
I03	2	0.576	0.603	1.04	4.48	Excellent	26
I04	2	0.576	0.703	1.22	19.34	Fair	38
I05	2	0.576	0.603	1.04	4.48	Excellent	25
I06	2	0.637	0.765	1.17	15.29	Good	31
I07	0.5	0.576	0.703	1.22	19.34	Fair	38
I08	1	0.586	0.727	1.24	19.39	Fair	37
I09	1.5	0.614	0.727	1.18	15.54	Good	32
I10	2	0.630	0.750	1.17	13.69	Good	33
I11	2.5	0.576	0.603	1.04	4.48	Excellent	26
I12	3	0.637	0.752	1.18	15.29	Good	33
I13	3.5	0.576	0.603	1.04	16.33	Fair	36
I14	0.0	0.576	0.703	1.22	19.34	Fair	37
WG1	4	0.621	0.746	1.20	16.8	Fair	37

Particle size

Measurement of particle size involves the electromagnetic sieve shaking of the sample through the series of successively arranged sieves (Sieve No. 20, 30, 40, 60, 80, 100 and receiver) and weighing the portion of the sample retained on each sieve and calculation of same.

Table 6.11: Particle size analysis of formulation batches

Batch No	sieve Number			
	20	**40**	**60**	**80**
I01	3.8	7.3	9.58	29.11
I02	4.3	8.6	12.56	31.88
I03	4.3	8.6	12.56	31.88
I04	5.3	10.76	15.12	32.43
I05	6.41	12.62	17.46	33.27
I06	6.40	12.56	16.46	28.56
I07	5.1	9.80	14.12	31.46
I08	4.2	8.5	12.56	30.90
I09	6.40	12.56	16.46	28.56
I10	3.8	7.3	9.58	29.11
I11	4.3	8.6	12.56	31.88
I12	4.3	8.6	12.56	31.88
I13	5.3	10.76	15.12	32.43
I14	6.41	12.62	17.46	33.27
WG1	3.1	5.8	12.58	28.64

Table: Formulations of Ibuprofen tablet 400mg

Batch No.	Composition											
	Drug (mg)	**Lactose DC (mg)**	**Aerosile (mg)**	**MCC (mg)**	**Starch (mg)**	**PVP K30 (mg)**	**Deprogel (mg)**	**Talc (mg)**	**Magnesium stearate (mg)**	**Moisture (%)**	**Time (min.)**	**RPM**
I01	400	60	4	80	60	16	12	0	8	q.s.	20	100
I02	400	**100**	8	12	60	16	16	4	4	q.s.	20	100
I03	400	120	5	12	56	14	16	4	3	q.s.	20	100
I04	400	128	5	20	50	10	20	5	2	q.s.	25	100
I05	400	139	4	20	50	10	20	5	2	q.s.	25	150
I06	000	361.4	10.4	52	130	26	52	13	5.2	q.s.	30	150
I07	400	139	4	20	50	10	20	5	2	0.0	30	150
I08	400	139	4	20	50	10	20	5	2	0.5	30	150
I09	400	139	4	20	50	10	20	5	2	1.0	30	150
I10	400	139	4	20	50	10	20	5	2	1.5	30	150
I11	400	139	4	20	50	10	20	5	2	2.0	30	150
I12	400	139	4	20	50	10	20	5	2	2.5	30	150
I13	400	139	4	20	50	10	20	5	2	3.0	30	150
I14	400	139	4	20	50	10	20	5	2	3.5	30	150
WG1	400	139	4	20	50	10	20	5	2	4.5	30	150

Formulation of tablets using most suitable approach of MADG

Ingredients mentioned in table 6.15 were used for the formulation of modified tablets of Ibuprofen by MADG process. The ingredients were weighted, mixed in geometrical order and compressed by 15.6 x 8 mm size punch to get a 100 tablets each weighing 650 mg using 14 station single rotary Rimak tablet compression machine.

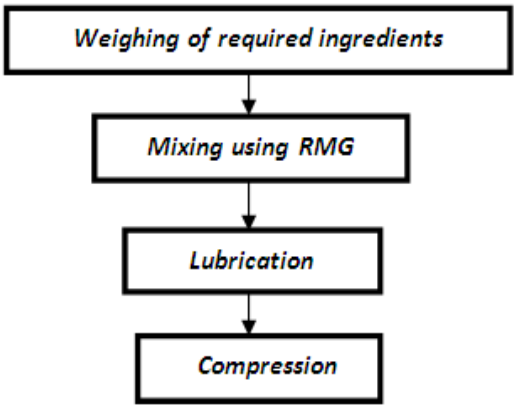


Fig. 6.19: Tablet manufacturing flow chart

Prior to compression the prepared granules were evaluated for pre-compression parameters (flow properties) viz. Angle of repose, Bulk density, Tapped density, Hausner's ratio and Compressibility index as per the procedure mentioned.

Appearance

Tablets were examined for texture, any surface flaws like cracks and chips.

Table: Characteristics of Batches

Sr. No.	Batch No.	Characteristic/observation				
		Appearance	Color	Taste	Thickness	Dimensions
1	**I01**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.7 mm	26 mm
2	**I02**	White color, Caplet shape, smooth, free from cracks	white	Bitter	5.7 mm	25 mm
3	**I03**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.7 mm	27 mm
4	**I04**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.8 mm	28 mm
5	**I05**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.8 mm	26 mm
6	**I06**	White color, Caplet shape, smooth, free from cracks	white	Bitter	5.8 mm	25 mm
7	**I07**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.8 mm	27 mm

8	**I08**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.8 mm	28 mm
9	**I09**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.8 mm	26 mm
10	**I10**	White color, Caplet shape, smooth, free from cracks	white	Bitter	5.8 mm	25 mm
11	**I11**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.7 mm	27 mm
12	**I12**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.7 mm	28 mm
13	**I13**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.7 mm	25 mm
14	**I14**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.7 mm	27 mm
15	**WG1**	White color, Caplet shape, smooth, free from cracks	White	Bitter	5.9 mm	28 mm

Dimensions

Dimensions such as thickness of the tablets were measured using digital Vernier caliper.

Weight variation

20 tablets of each formulation batch were weighed individually using an electronic balance. The average weight was calculated and individual tablet weight was then compared with average value and the deviation was recorded.[51]

Friability

$$\% F = (W_o - W) / W_o \times 100$$

Where, F = friability ***W_o = initial weight of the ten tablets*** W = final weight of the ten tablets

Disintegration time (*in vitro*)

The disintegration time was determined by using USP tablet disintegration test apparatus using 900 ml of deionised water without disk. For this, 6 tablets of each formulation were used and the disintegration test was conducted at following test conditions.

Hardness

Drug content

Two tablets of each formulation were used. The tablets were weighed and crushed. A quantity of powder equivalent to 650 mg of Ibuprofen was accurately weighed and transferred to 100 ml volumetric flask to which small volume of Phosphate buffer pH 7.2 was added to disperse the contents. Final volume was adjusted to 100 ml using Phosphate buffer

7.2. The dispersion was stirred for 2 hr using magnetic stirrer and then allowed to settle. Solution was filtered through Whatman filter paper (No.41). Appropriate dilution of filtrate was made using Phosphate buffer pH 7.2 and the UV absorbance was recorded.[55]

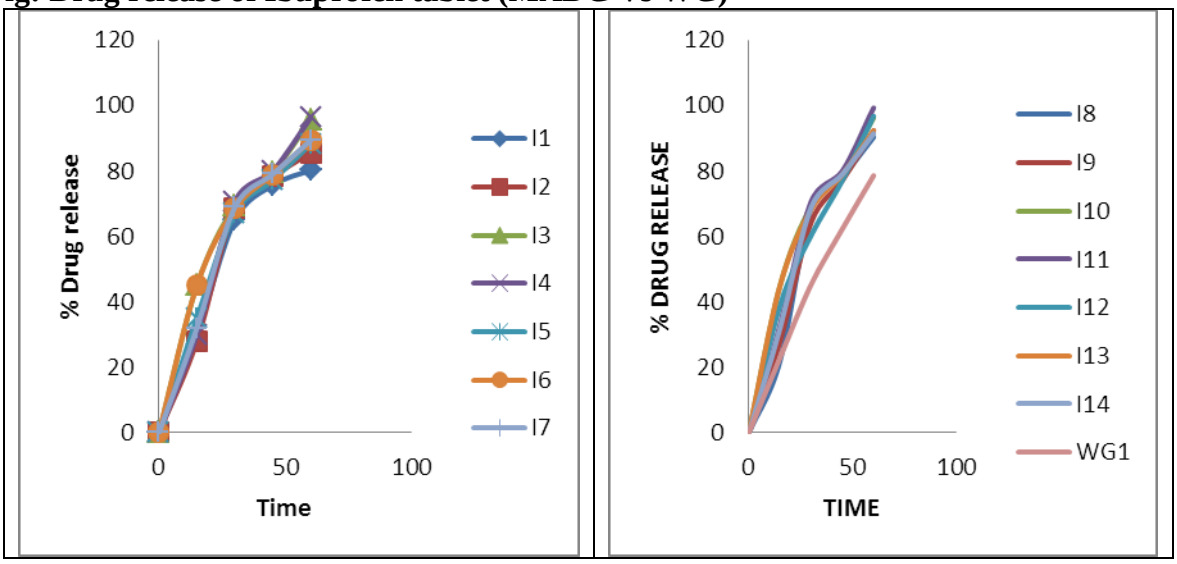
Drug release study (*in-vitro*)

i) Drug release of Ibuprofen in phosphate buffer pH 7.2

Table 6.14: Drug release of Ibuprofen in phosphate buffer pH 7.2

Batch no.	WEIGHT VERIATION	HARDNESS	Disintegration time	Drug content	Drug release	FRIABILITY
I01	0.651±5	111	64	95.30	80.30	0.1
I02	0.652±5	112	72	96.45	85.60	0.2
I03	0.645±5	90	78	96.22	95.60	0.3
I04	0.653±5	86	65	98.00	96.30	0.1
I05	0.655±5	72	63	97.38	88.30	0.4
I06	0.650±5	69	68	90.23	89.30	0.3
I07	0.651±5	48	78	96.45	89.36	0.2
I08	0.640±5	50	70	88.68	90.36	0.4
I09	0.643±5	70	65	95.40	92.36	0.3
I10	0.646±5	96	60	89.30	96.30	0.2
I11	0.650±5	110	55	99.20	99.30	0.1
I12	0.651±5	90	50	98.30	96.78	0.2
I13	0.653±5	97	20	86.40	92.33	0.3
I14	0.651±5	30	78	87.46	91.40	0.5
WG1	0.652±5	67	180	85.30	78.60	0.2

Fig: Drug release of Ibuprofen tablet (MADG Vs WG)



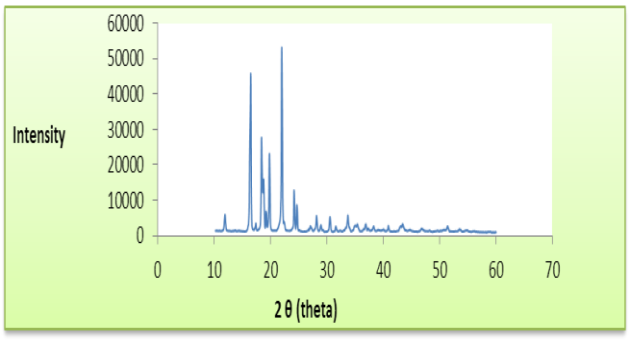


Fig 6.13: X- ray diffraction spectrum of Ibuprofen

The analysis of XRD pattern reveals sharp intensity of the crystallinity peaks of the pure drug, but when it was incorporated into the excipients the intensities of the peaks were decreased due to decreased crystallinity of the drug. The formulation containing MCC and Lactose DC showed maximum amorphisity. XRD analysis showed that there was little reduction in the crystallinity of drug when formulate these polymers

Differential Scanning Calorimeter

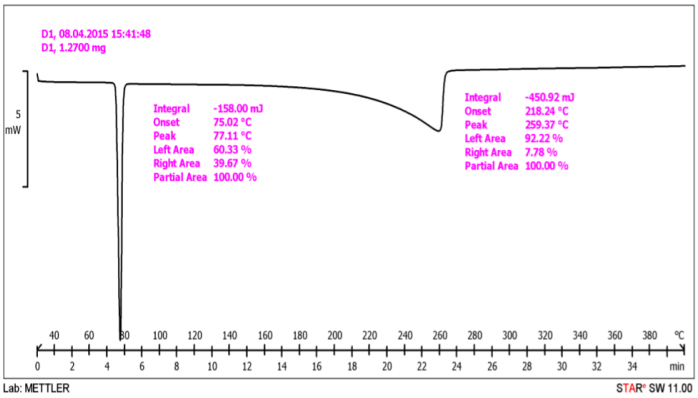


Fig. 6.14: DSC formulation graph

The thermo gram of pure Ibuprofen showed sharp endothermic with melting peak at 77.31ºC. Thermo gram of In optimized formulation showed peak at 77.11ºC. Slight shift in of endothermic peaks on left hand with decreased in its intensity indicates little amorphization of drug shown in Figure.

This may attributed to presence of moisture which may cause drug in crystallization form and hence reduces drug dissolution which may results in decreased release of Ibuprofen.

FTIR

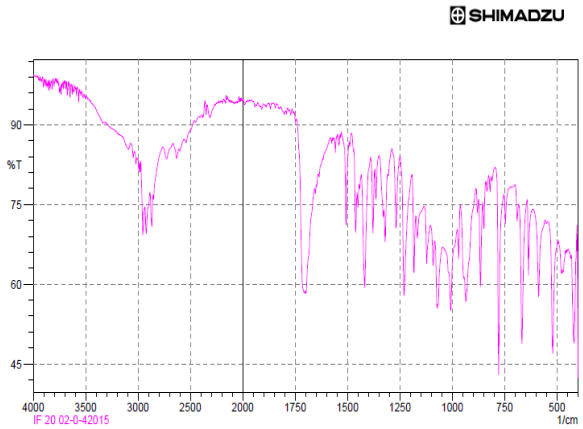
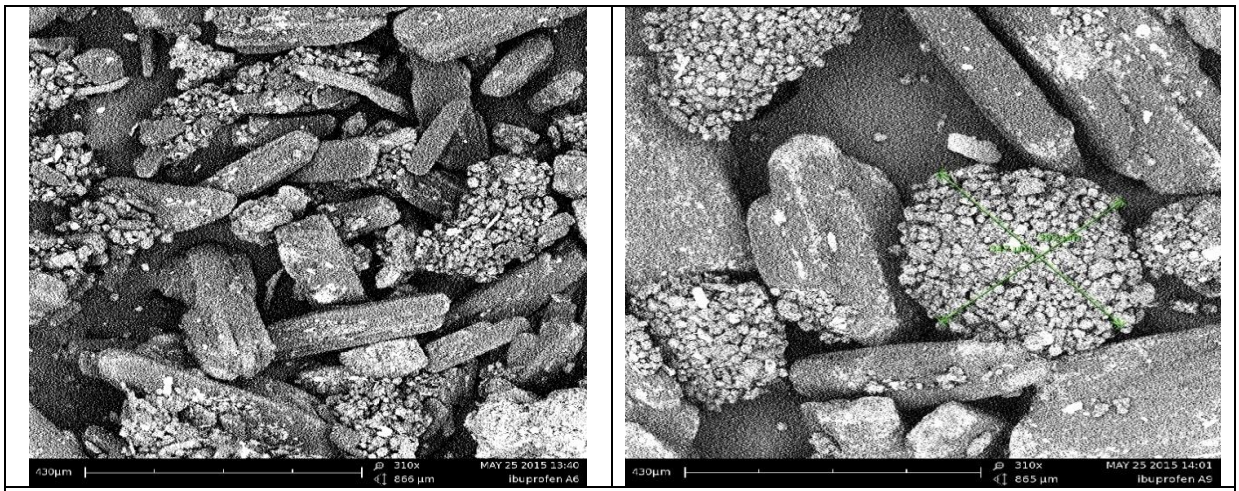


Fig. : FTIR formulation graph

FTIR spectrum of Ibuprofen showed peaks at 945.94 due to O-H bending, 1258.72 due to C-O stretching, 1378.69 due to CH2 and CH3,1417.65 due to Ar C-C stretching and 1700.98 due to C=O stretching. The optimize formulation showed more intense and prominent peaks.

SEM Analysis

Scanning electron microscopy was performed to study the effect of mixing time on the morphology of particles. Figure shows the scanning electron micrograph of initial blend of Ibuprofen and binders. Result was determine as per procedure and SEM of drug, placebo and formulation show following



C:Batch F4

Fig: SEM formulation and placebo graph

DISCUSSION

Rheumatoid arthritis, osteorthritis and other musculoskeletal major disorder in India. Ibuprofen has a local action in larg intestine as it is used in the treatment of Rheumatoid

arthritis, osteorthritis and other musculoskeletal disorder. Ibuprofen primarily absorbed from lower part of gastrointestinal tract. The main objective of the study was to develop, evaluate and optimization of tablets containing poorly water soluble drug by moisture activated dry granulation method, thereby reducing the production cost of tablet.

Appearance, melting points, loss on drying, λ_{max}, IR study and DSC study of drug Ibuprofen were carryout as per the specification of B.P. It was observed that the obtained sample of Ibuprofen complies with the standard of quality mentioned in B.P. Standard calibration curve of Ibuprofen (absorbance Vs concentration) was found to be linear and obeyed Beer Lambert's law in the range of 0-10µg/ml. SSG and povidone were evaluated for their standard. It was observed that they complies with the standard of quality as per prescribe official books.

Preliminary batches of Ibuprofen tablets were prepared by moisture activated dry granulation method using sodium starch glycolate as Superdisintegrant and povidone as binder polymer in various concentrations. From the results of preliminary batches, it was observed that polymer concentration is important parameter in the formulation of tablets. As the SSG concentration was increased from 12 mg to 20 mg, and concentration of povidone were increased from 10 mg to 16 mg disintegration time, % drug release from tablets were increased. The disintegration time was decreased with the decrease in the quantity of sodium starch glycolate in tablets by moisture activated dry granulation process

CONCLUSION

Ibuprofen tablets were successfully developed using moisture activated dry granulation method. Concentration of sodium starch glycolate 2.8% and concentration of povidone 0.8% was taken then resultant tablets were given drug release (85.60±0.36) in 15 minutes. The *in-vitro* results indicated that the tablets were potentially useful. The moisture activated dry granulation method was found to be simple, reproducible, easily controllable, economical, and continues process. Additionally, the excipients used for the formulation of tablets were cheap and easily available. Other drugs for the use in moisture activated dry granulation method can be incorporated in the formulation of tablets. Therefore, these types of moisture activated dry granulation method for tablets can be commercially processed easily and potentially better other than wet granulation method for formulation of tablets.

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