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Optimization of crystallo- Co- Agglomerates of meloxicam-paracetamol to improve flow properties and dissolution

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Abstract
The purpose of this research was to obtain directly compressible agglomerates of Meloxicam-Paracetamol containing desired ratio of drugs using a crystallo – co- agglomeration technique. Crystallo-co-agglomeration is an extension of the spherical crystallization technique, which enables simultaneous crystallization and agglomeration of two or more drugs or excipients. Acetone-water system containing Polyvinylpyrrolidone (PVP) and Hydroxypropyl methyl- cellulose E5 (HPMC) as a additive were used in crystallization system. Acetone acted as a good solvent as well as bridging liquid for Meloxicam-Paracetamol for agglomeration. Meloxicam was crystallized from acetone and agglomerated with Paracetamol. Excipient compatibility study was carried out by FTIR. Selection of polymer is carried out by drug content, flow properties, % drug release and Heckel analysis. The optimization of formulation of selected polymer was carried out by using 2^3 factorial design. Where the factors were speed of rotation, polymer: drug ratio and amount of bridging liquid. The responses evaluated were % drug release, MYP and carrs index. Evaluation of optimization was carried out. The compatibility study for optimized batch and pure drug was done by powder X ray difractometry (PXRD), FTIR and surface morphology was done by scanning electron microscopy (SEM) The result revealed that micromeritic properties (angle of repose 19.73-28.07^0, % compressibility 9-17 and Hauser ratio between 1.08-1.20 and compactibility (mean yield pressure 1.08-3.99 tonns) of agglomerates of PVP enabled direct compression without any defect. PXRD showed no change in crystalline form of drug and SEM demonstrated spherical and smooth surface. *In vitro* dissolution study revealed that varying the polymer concentration prolongs the drug release. From the results, the conclusion is that crystallo-co-agglomeration technique is a suitable alternative method to the granulation process and can be used for design of immediate release Meloxicam-paracetamol agglomerates with varying concentration of polymer.

Keywords: Crystallo-co-agglomeration, meloxicam, paracetamol, bridging liquid, dissolution, flowability

1. Introduction
Tablet is the most popular dosage form of all pharmaceutical preparations due to higher rate of manufacture and economy achieved. Direct compression is the most efficient process used in tablet manufacturing because it is the fastest, simplest and least expensive tablet-compression procedure. The material used for the direct compression of tablet should be in physical form that flows smoothly, directly compressible and physically stable so as to achieve rapid production capability of tablet formulation. To impart these properties the drugs are subjected to particle design techniques, spherical crystallization is one the techniques of particle design [1-3].

Kadam *et al*. has described the crystallo-co-agglomeration (CCA) technique, which was designed to overcome the limitations of spherical crystallization. It is a modification of the spherical crystallization technique in which a drug is crystallized and agglomerated with an excipient or with another drug, which may or may not be crystallized in the system. The agglomeration is performed using bridging liquid [4, 5]. The process enables design of agglomerates containing two drugs or drug in combination with diluent. Recently, Pawar *et al*. reported preparation of agglomerates containing paracetamol with ibuprofen and ibuprofen with talc by CCA technique [6, 7]. Difference in the physicochemical properties of the drug molecules and the excipients presents major challenge in the selection of a solvent system for the crystallo-co-agglomeration.

The present work describes formation of agglomerates of meloxicam and paracetamol to enhance flow, compression and dissolution properties of combination. A 2^3 factorial design was employed where stirring speed, polymer drug ratio and volume of bridging liquid were optimized to achieve the agglomerates that will have required flow, compression ad drug release properties.

2. Material and Method

2.1 Materials

Meloxicam was gift sample from Sankalp Healthcare and Allied Products PVT.LTD and Paracetamol from Cipla Ltd. (Mumbai). Hydroxypropyl methylcellulose (HPMC K 100 M) and Polyvinylpyrrolidone (PVP) was supplied by Loba chemicals, Mumbai. Acetone and all other chemicals, which are of analytical grade, were procured from Loba Chemie Ltd., Mumbai.

2.2 Method

Crystallo-Co-Agglomeration Technique [8]

Meloxicam (3.25 g) and polymer (PVP) was dissolved in good solvent (acetone). Paracetamol (0.75 g) and HPMC was uniformly dispersed in water (bad solvent). The two solutions were mixed with stirring at 800 rpm under overhead stirrer. The temperature of the crystallization system was maintained below 5 ^{0}C and stirring for about 15 min by the end of which agglomerates were obtained these were then filtered and dried over-night.

3. Formula optimization

A three factor two level 2^3 factorial design was selected for optimization where the 3 factors were, polymer: drug ratio (A), stirring speed (B) and amount of bridging liquid (C). The response to be optimized were % drug release, Mean yield pressure (MYP) and Carr index. The data obtained was analyzed using Design Expert trial version 10.

Table 1: Coded levels translated in actual units.

Coded level	Actual value in %		
	A	B	C
-1	0.5:1	600 rpm	2ml
+1	1.5:1	800 rpm	4ml

4. Evaluation of cryallo co agglomerates

4.1 Determination of drug content [9]

Drug content was determined by dissolving samples of Crystallo-co-agglomerates (10 mg) in 10 ml of acetonitrile. The solution was filtered through Whatman filter paper no. 41, and was suitably diluted the absorbance was measured at 360 and 257 nm respectively using double beam UV spectrophotometer (Jasco 550, Japan).

4.2 Micromeritic Studies [10, 11]

The flow properties of meloxicam, paracetamol bulk and agglomerates were determined in terms of angle of repose, bulk density, Carr Index and Hausner ratio. Angle of repose was determined by fixed funnel method whereas Carr Index and Hausner ratio were calculated from bulk density and tapped density using methods described in literature.

4.3 Heckel Anlysis [12]

Heckel equation is expressed as:

$$\ln(1/(1-D)) = kP + A \quad \text{------ Eq 1}$$

where,

D= relative density of a powder compact at pressure P

K= the slope

P= pressure

A= related to the die filling and particle rearrangement before deformation and bonding of the discrete particles which is a function of the initial bulk volume.

The Heckel analysis was performed on bulk drugs and agglomerates using discs prepared at compaction pressure of 2,4,6,8,10,12 tonnes in KBr press(technosearch instruments,Model-M-15) using 13.00 mm flat faces punches, the diameter, height, and weight of the tablets was measured and Heckel analysis was performed by plotting log relative density vs pressure.

4.4 *In-vitro* studies [13]

The bulk drug combination and agglomerates equivalent to (325 mg of paracetamol and 7.5 mg of meloxicam) were subjected to dissolution rate studies in USP type II dissolution apparatus (Model TDT-08L, Electrolab) in 900 mL of 0.2 M phosphate buffer (PH 7.4) maintained at 37±0.5 °C, at 75 rpm. Samples were withdrawn at appropriate time intervals, immediately filtered through 0.45 µm membrane filter, suitably diluted and analyzed spectrophotometrically at 243 and 261.8 nm.

4.5 Powder X-ray diffractometry (PXRD) [14]

The PXRD data of Crystallo-co-agglomerates of optimized batch and paracetamol-meloxicam were recorded on a Bruker PXRD (Model: D 8 Advance) with copper target. The conditions were: 40 kV voltages; 40 mA current; at room temperature. The samples were loaded on to the difffractometer and scanned over a range of 2θvalues form 10 to 80^0 at a scan rate of 0.05^0 /min.

4.6 Scanning electron microscopy (SEM)

The surface morphological properties of Crystallo-co-agglomerates of optimized batch and pure drug was investigated by scanning electron microscopy (SEM-Jeol Instruments, JSM-6360, and Japan). Samples were mounted on a double-faced adhesive tape, sputtered with gold. Scanning electron photographs were taken at an accelerating voltage of 20 kV and obtained micrographs were examined at ×100, magnification.

4.7 Preparation and evaluation of Meloxicam-Paracetamol tablet using agglomerates [15, 16]

The agglomerates were subjected to direct compression after addition of different excipients table. Evaluation of tablet such as thickness and diameter, hardness, friability, weight variation, disintegration time and dissolution was carried out by using methods reported in literature.

Table 2: Formula for preparation of tablet using agglomerates

S. No	Ingredient	Quantity (mg)
1	Tinidazole crytalllo co agglomerates	202
2	Starch	70
3	Lactose	120
4	Magnesium state	8

#Total weight of the tablets was kept 400 mg

5. Result and Discussion

5.1 Drug Excipient Compatibility

The FTIR spectrum of Meloxicam and Paracetamol (table 3) respectively was recorded and compared with that of the standard in the literature.[17,18] The major peaks of meloxicam and paracetamol could be seen as mentioned in table no 2 while there was absence of any new peak. From this it can be concluded that there is absence of any well-defined interaction between drug, diluents and polymers. Hence drug - excipients compatibility was established.

Table 3: The functional groups in FTIR spectrum of Meloxicam and Paracetanol

Interpretation of meloxicam		Interpretation of paracetamol	
Wave number (cm^{-1})	**Functional group**	**Wave number (cm^{-1})**	**Functional group**
3286	Sec. amine(strech)	3360	N-H stretching
3091	C-H(stretch aromatic)	3300	O-H stretching
2911	(C-H stretch, aliphatic CH3 sym)	3090	Aromatic C-H stretching
1620	NH2 (scissoring vibrations)	1800	=C-H bending
1536	(C = N stretch)	1650	C=O stretching
1150	S=O (strech).	1600	Aromatic C=C stretching
		1570	N-H bending

5.2 Crystallo-Co-Agglomeration Technique

Meloxicam anti inflamatory and paracetamol anantipyretic, both are poorly water soluble and processes poor compaction and flow properties. The agglomerates of meloxicam-paracetamol were prepared using a crystallo co agglomeration technique by crystallization from acetone-water system and agglomerated in presence of hydrophilic polymer PVP. The drugs in solution containing HPMC were crystallized and the bridging liquid (acetone) led to agglomeration in presence of PVP, the agglomerates were stirred to provide spherical shape while formation of liquid bridges led to strengthening of agglomerates.

5.3 Drug content

The percentage drug content of meloxicam and paracetamol in crytallo co agglomerates of optimization run was found to be between 99% and 100%.

5.4 Micromeretic studies

Micromertic properties of the crystallo co agglomerates was studied in terms of bulk density, tapped density, Carr index, Hausner ratio and angle of repose. Meloxicam and paracetamol bulk had a significantly higher angle of repose ($>35^0$) which indicates irregular shape of the crystals where as that of crystallo co-agglomerates were seen to have angle of repose between (19.73-28.07) (Table 4). The Carr index and Hausner ratio of agglomerates ranged between (8.03-17.00) and (1.08-1.20) respectively compared to that of bulk meloxicam and paracetamol (22.96%, 34.78) and (1.29, 1.56) respectively. This indicates improvement in the flowability of the agglomerated crystals. The reason for the improved flow of agglomerates is the significant reduction in the inter particle friction because of the nearly spherical shape and the larger size of the crystals.

5.5 Heckel Analysis

Heckel analysis has been used to classify powders as their compaction behavior and for the interpretation of the mechanism of bonding. Mean yield pressure (Py) is the pressure required to deform a powder or granules and to obtain compacts and is defined as the inverse of slope of the linear portion of the Heckel plot. The slope (k) is an indication of the deformation behavior of the material. With low values of Py, the amount of plastic deformation increases and when high values of Py is an indication of the material compressing behavior is mainly fragmentation. The values obtained from Heckel equation as shown in (Table 4) indicated significant low mean yield pressure (Py) of spherical agglomerates (1.08-3.99 ton) than plain Meloxicam (5.6 tons) and Paracetamol (5.4 tons) indicating improvement in compaction behavior of spherical agglomerates.(table no 4)

5.6 *In-vitro* studies

Dissolution studies of which products 8 optimization batches

In *In-vitro* dissolution study of spherical agglomerates showed significantly faster drug release profile (92.00, 93.17%) of meloxicam and paracetamol as compared with plain meloxicam and paracetamol (35% and 55.4%) respectively in 1 h. The reason for this faster drug dissolution was linked to the increase in surface area, wetting meloxicam-paracetamol agglomerates, showed better wettability due to addition of hydrophilic polymer and the porous internal structure resulted in faster dissolution. (table no 4)

Table 4: Drug content, Myp, Carr index, % release of Crystallo co agglomerates prepared in 8 batches. By varying three factors (stirring speed, polymer: drug ratio, amount of bridging liquid) at two levels.

Formulation code	Polymer: drug ratio (g) (A)	Stirring speed (rpm) (B)	Amount of bridging liquid (ml) (C)	Hausner ratio	Carr index (%)	Angle of repose (θ°)	Myp (tonnes)	% release	
								Meloxicam	Paracetamol
1	0.5:1	600	2	1.10	9	20.57	2.14	86.63	81.07
2	1.5:1	600	2	1.14	12.5	23.62	3.18	70.05	72.42
3	0.5:1	800	2	1.08	8.03	19.73	1.08	91.00	88.34
4	1.5:1	800	2	1.10	9.12	20.66	2.97	77.92	78.12
5	0.5:1	600	4	1.11	10.5	21.80	3.11	87.32	84.94
6	1.5:1	600	4	1.20	17.0	28.07	3.99	71.2	72.42
7	0.5:1	800	4	1.09	8.05	20.22	1.89	92.0	93.17
8	1.5:1	800	4	1.12	11.8	22.37	3.13	79.16	80.03
Meloxicam	-	-	-	1.29	22.96	36.50	5.6	35.00	-
Paracetamol	-	-	-	1.56	34.78	38.65	5.4	-	55.4

5.7 Optimization using Design Expert, State-Ease, Minipollis MN

5.7.1% release of meloxicam and paracetamol

The % deug release is most coveted characteristic of a drug material; dissolution of meloxicam and paracetamol was highly reduced by increasing polymer content as agglomerates formed were sticky in nature. The low stirring speeds which produce bigger agglomerates may also reduce the dissolution. The higher polymer: drug ratio and low bridging lead to significant reduction in dissolution. High bridging liquid and high stirring speed show increase in dissolution. Also a combination of low polymer: drug ratio and high stirring speed lead to increase in dissolution. (Fig 1, 2) Incorporation of PVP causes faster consolidation and yields particles with lower tortuosity and hence batches containing PVP at higher levels exhibit slower release of drugs.

Equation for % release of Meloxicam and paracetamol

$$\%\ \text{release of meloxicam} = +81.91 - 7.33A + 3.11B - 0.51C + 0.85AB + 0.088AC + 0.050BC$$

$$\%\ \text{release of paracetamol} = +81.31 - 5.57A + 3.60B + 1.33C - 0.27AB - 0.85AC + 0.36BC$$

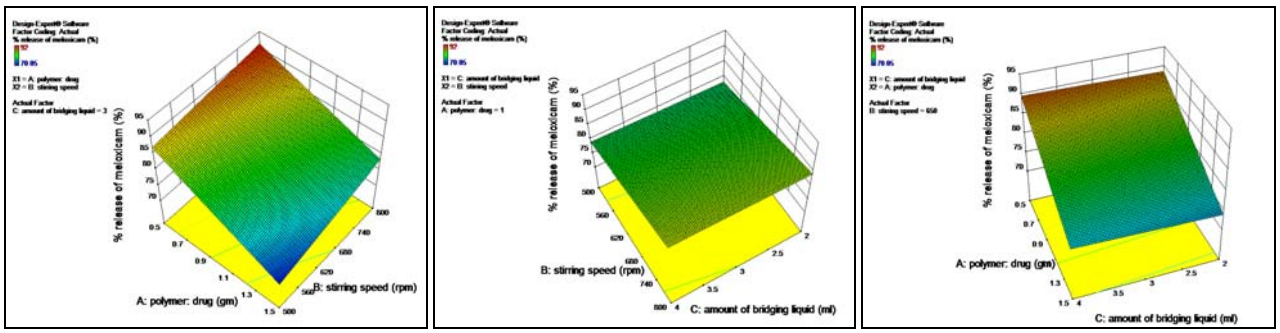

Fig 1: Response surface plot for % release of meloxicam

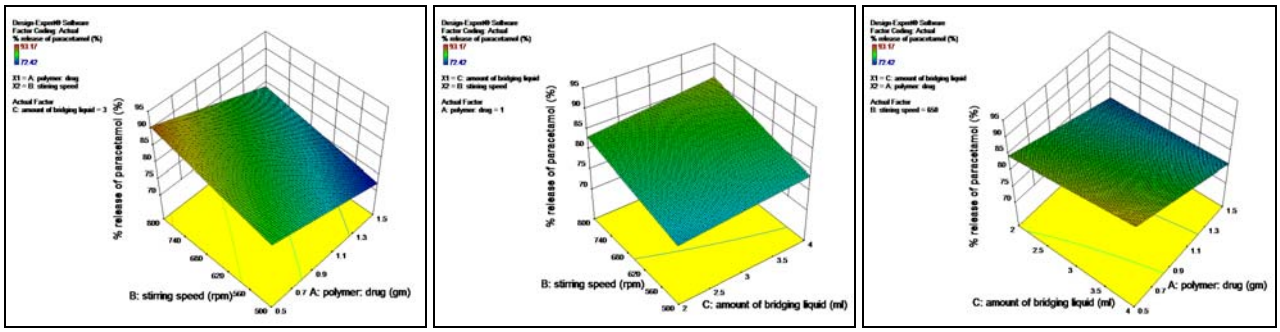

Fig 2: response surface plot for % release of parcetamol

5.7.2 MYP

The mean yield pressure values of cystallo co agglomerates were found to be higher at high polymer and high bridging liquid concentration, whereas at low values of polymer the increase in bridging liquid reduced MYP sharply which may be due to porous agglomerates whereas PVP being soft and plastic in nature gives better compressibility to the formed agglomerates as it undergoes plastic deformation. The stirring speed did not have appreciable effect on MYP hence was excluded from equation. The combination of low bridging liquid and high stirring speed reduced the MYP as the particle collisions increase at high speed which resulted in smaller particle size and smaller MYP. (Fig. 3)

The binary combination of variables as well as all the three demonstrated a good effect on reducing the MYP

Equation for MYP= $+2.76 + 0.71A - 0.50B + 0.26C + 0.071AB - 0.18AC - 0.026BC$

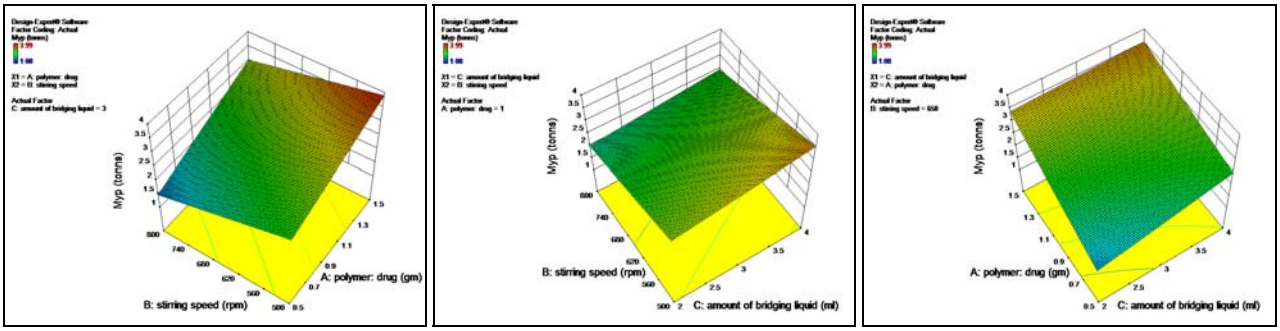

Fig 3: response surface plot for MYP (tons)

5.7.3 Carr index

Carr index was reduced by increasing the polymer and increased to some extent by stirring speed. The bridging liquid had highest influence on increasing the Carr index, Optimum Carr index values (8.33-14.8%) were seen at high stirring speeds and bridging liquid combination, the values declined with decrease in either of the variables. Whereas low polymer and high bridging liquid combinations exhibited good Carr index. (Fig 4)

Equation for Carr index = $+10.75 + 1.86A - 1.50B + 1.09 - 0.65AB + 0.71AC - 0.41BC$

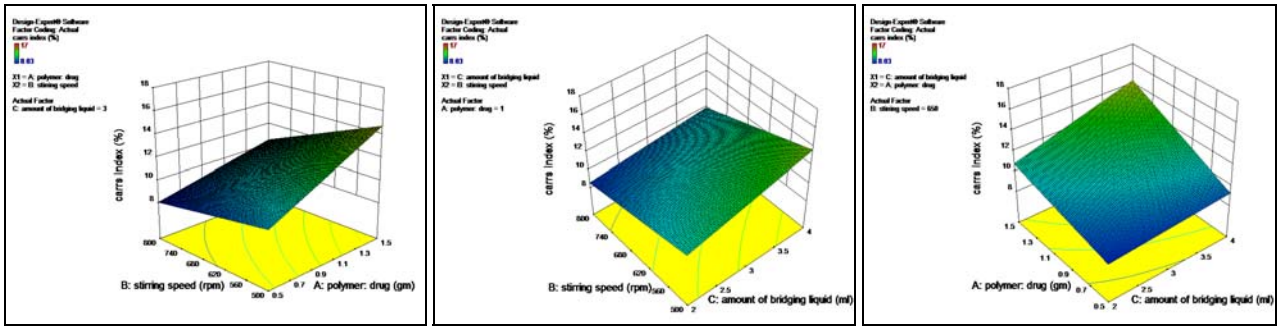

Fig 4: response surface plot for carr index

5.8 PXRD

The PXRD scan of bulk Meloxicam and Paracetamol (In fig 5 A,B) respectively showed intense peaks of crystallinity, whereas the XRD pattern of agglomerates (In fig C) exhibited halo pattern with less intense and denser peaks compared with plain Meloxicam and Paracetamol indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form.

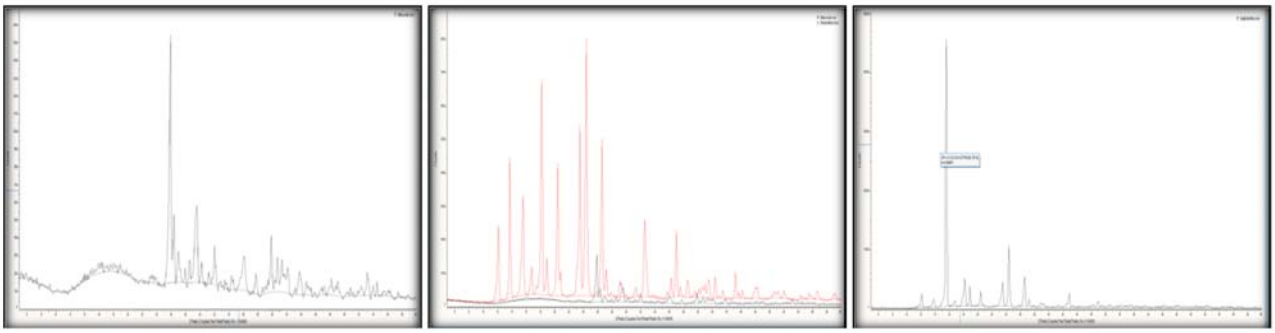

Fig 5: A. PXRD of Pure drug (Meloxicam), B. PXRD of Pure drug (Paracetamol), C. PXRD of Agglomerates of optimized batch.

5.9 Scanning Electron Microscopy

The Meloxicam and Paracetamol in fig 6 (Fig A, Fig B) particles in the physical mixture were irregular and the shape of prepared agglomerates (Fig C) is uniform and spherical. .The reason for the improved flow of agglomerates is the significant reduction in the inter particle friction because of the nearly spherical shape and the larger size of the crystals

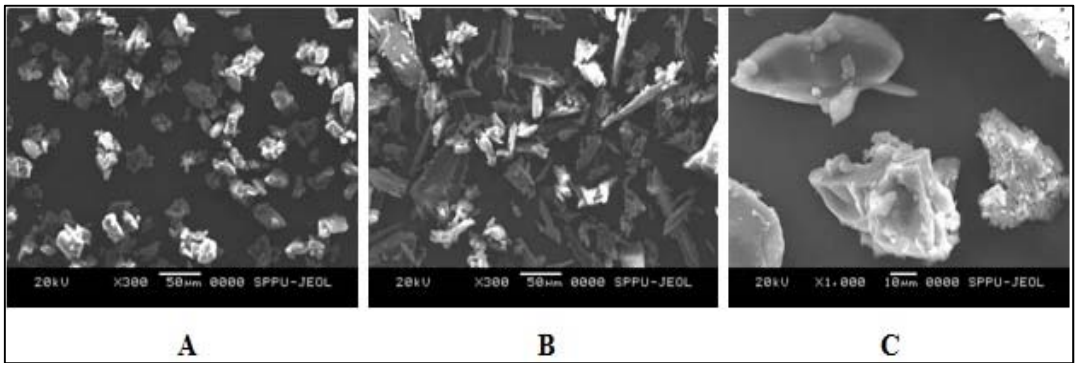

Fig 6: Scanning electron micrographs. A: Paracetamol powder (×300), B: Meloxicam powder(x300) C: Agglomerates of optimised batch (×1000)

5.10 Preparation and evaluation of Meloxicam-Paracetamol tablet using agglomerates [17, 18]

Tablets are prepared by using formula given in table no 2 and evaluation was carried out.

5.11 Results of evaluation of tablet

Tablets are prepared by using formula given above in table 2. it shows that diameter and thickness was 10.00 mm and 5.00 mm respectively. Hardness was found to be within limit 3.8-4.0 kg/cm^3. The average friability was found to be 0.44% which is within limit of 1% as per IP. Average weight of 20 tablets was found to be 0.355 g. The limit for deviation is 0.355±0.027. All the tablets are within the limits hence all tablets comply as per IP which states not more than 2 tablets should be outside the limit.

5.12 *In vitro* -Disintegration test

The disintegration time was found to be 13.00 min.

6. Conclusion

The crystallo-co-agglomeration process was optimized with respect to the variables such as polymer drug ratio, stirring speed and amount of bridging liquid. It was seen dissolution increases with decreasing polymer content, increasing stirring speed, and increasing bridging liquid. The required Carr index could be achieved at lower polymer, high speed and low bridging liquid. The MYP was increased the most by polymer, bridging liquid and decreased with rotation speed.

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