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Preparation and Optimization of Directly Compressible Excipient Using Design of Experiment Approach

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KEYWORDS

Co-processed excipient, spray drying, factorial design, zaltoprofen, mannitol, microcrystal line cellulose

ABSTRACT:

Introduction: Excipients are a vital part of any pharmaceutical formulation which also effects its efficiency. To improve the formulation aspects an excipient with desired characteristics is required. There is always a need for better excipients to improve the formulation parameters which makes excipient improvement research inevitable. As it is very difficult to develop new excipient, co-processed excipients can fill the gap.

Objective: In the present study the aim is to develop an optimized novel co-processed excipient of mannitol and microcrystalline cellulose using spray drying technique.

Methods: In the present study microcrystalline cellulose and mannitol are chosen as excipients to be co-processed by spray drying process. 32 factorial design was applied to develop an optimized co-processed excipient which is then compressed in tablets by incorporation of drug zaltoprofen. The tablets are then subjected to various evaluation parameters.

Results: It has been found that the particle size of co-processed excipient of microcrystalline cellulose and mannitol was found to be 212 ± 2.2 µm and the dilution potential was found up to 80%. Disintegration time of prepared tablets was less than 8 minutes and in vitro drug release of optimized batch was 95% in 25 minutes.

Conclusions: The optimized co-processed excipient using factorial design approach was successfully prepared and found to be superior in all the properties as compared to physical mixture. The zaltoprofen tablets have shown a release of 95% within 25 minutes.

1. Introduction

Pharmaceutical excipients are the ingredients other than the active drug which are required to formulate a stable and effective medicinal preparation[1]. Excipients aids in improving bioavailability along with support in manufacturing process and protection from environmental factors. There is always a need to look out for better excipients which would improve formulation characteristics without altercating the desired outcomes[2].

Direct compression of excipients is a simple, scalable and cost-effective technique of tablet formulation in which ingredients can be compressed directly into acceptable tablets. The excipients required for direct compression should possess good flowability and compressibility. Direct compression offers advantage of faster dissolution and better stability, as the tablet is less prone to microbial growth due to absence of granulating liquid[3].

Co-processing of excipients is a technique in which two or more excipients are fabricated in such a way that their physical properties such as flowability, compressibility get modified which is not achieved by simple physical mixing. Co-processing makes the excipients suitable for direct compression which cannot be achieved in a superior way by use of a single excipient[4]. Thus to achieve good physico-mechanical properties of excipients co-processing remains a matter of research to get better drug product[5].

Zaltoprofen is a nonsteroidal anti-inflammatory drug (NSAID) which is preferential COX-2 inhibitor having anti-nociceptive properties. It is a potent analgesic used for treatment of rheumatoid arthritis, osteoarthritis, post-operative surgical pain and chronic inflammation. Zaltoprofen is a BCS Class II drug and possess poor

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aqueous solubility thus low dissolution rate. Formulation of fast dissolving tablets of zaltoprofen can help to overcome poor solubility and can aid in faster dissolution[6].

2. Objectives

Microcrystalline cellulose (MCC) has superior strength and cohesiveness due to hydrogen bonding between adjacent cellulose molecules. Even under low compression forces MCC has ability to form strong compact[7]. Mannitol is a filler/binder of choice due to its low hygroscopicity and its negligible effect on blood sugar levels as compared to other diluents[8]. The aim of the present study is to investigate the effect of different combinations of MCC and mannitol on co-processed excipient and on dissolution characteristics of directly compressed zaltoprofen tablets.

3. Methods

3.1 Materials

The drug zaltoprofen was obtained as a gift sample from Ipca Laboratories, Ratlam, India. The microcrystalline cellulose and mannitol was purchased from Loba Chemie. Distilled water used was prepared In house.

3.2 Preliminary studies

Preliminary studies were conducted to determine process parameters and to optimize the ratio of MCC and mannitol. Different ratios of MCC and mannitol previously passed through sieve number 80, were weighed and dispersed in distilled water at 25°C to form a slurry. The slurry was well stirred using magnetic stirrer (Remi Elektrotechnik, India) for 15-20 minutes to ensure complete wetting of powder particles. The flow of slurry through nozzle without any hindrance was considered as deciding factor for total solid content. It was observed that more than 5% w/w of solid content showed resistance in passage through nozzle. Hence solid content up to 5% w/w is considered as uppermost limit for the MCC and mannitol slurry. The feed rate and aspiration rate was set to 2 mL/minute and 55 Nm3/hour. The atomization pressure was kept at 1 bar[9].

3.3 Excipient preparation

MCC and mannitol were co-processed using spray drying technique. The dispersions were then spray dried using LU222 Advanced spray dryer (Lab Ultima, India). The slurry was fed at a pre-determined rate to the fluid nozzle by the aid of peristaltic pump and co-current spray air contact. The slurry was stirred continuously throughout the process by aid of magnetic stirrer to ensure uniformity in dispersion[10].

3.4 Experimental design

A 32 full factorial design was used to study the effect of different ratios of MCC: mannitol and process parameters on determinant attributes of co-processed excipient. The independent variables selected are inlet temperature and ratio of MCC:Mannitol (MC:MA). The response variables chosen were angle of repose, Carr's index, Hausner's ratio and percentage yield[11]. The formula for experimental design batches is shown in Table 1.

3.4.1 Angle of repose

Angle of repose is defined as the steepest slope made by a powder heap on a surface when allowed to flow freely. Angle of repose was determined by fixed funnel method. The powder is allowed to flow freely from a funnel fixed at a certain height on a graph paper placed on an even horizontal surface. The angle of repose (θ) was then calculated using the formula[12]:

$\theta = \tan^{-1} h/r$

Where, h: Angle of repose, h: height of the pile (cm) and r: radius of the base of the pile (cm).

3.4.2 Bulk and tapped density

A measuring cylinder of 100 mL capacity was taken and filled with co-processed excipient powder up to a definite height. This volume occupied by the powder is known as bulk density. The cylinder was then tapped from a height of 2 inches for 500 times, the resulting compacted volume is known as tapped density. Both bulk and tapped densities were then recorded[13].

3.4.3 Carr's index

It is the percentage ratio of difference in tapped density and bulk density to tapped density[14].

Carr's Index= [(Tapped Density-Bulk Density)/ Tapped Density] X 100

3.4.4 Hausner's ratio

It is the ratio of tapped density to bulk density and is highly correlated with the flowability of powder[15].

Hausner's ratio = Tapped density/Bulk density

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Table 1: Experimental design batches as per 32 full factorial design

Run order	Batch	Coded values		Decoded values	
		MC: MA	Inlet air temperature (°C)	MC: MA (%w/w)	Inlet air temperature (°C)
1	C3	3	2	1:4	230
2	C4	3	1	1:3	230
3	C1	1	1	1:4	200
4	C6	1	2	1:3	170
5	C8	1	3	1:2	230
6	C2	2	2	1:4	200
7	C9	3	3	1:2	200
8	C5	2	3	1:3	170
9	C7	2	1	1:2	170

3.5 Characterization of optimized co-processed excipient

3.5.1 Heckel's plot

Heckel's equation is used to ascertain the compaction characteristics of powders and granules. The compaction behaviour of co-processed excipient and physical mixture was analysed using Heckel's equation. powder (500±5 mg) was compressed in a Kbr press using a 1.3cm flat faced punch and matching die at pressures of 50, 100, 125, 150 and 200 kg/cm2 for 1 min. The weight, diameter and thickness of the compacts were determined. The compacts were then stored over silica gel for 24 hours. The data was then processed using Heckel's equation. The mean yield pressure (Py) was obtained by regression analysis of the linear portion of the plot[16].

$$\ln(1/e) = Pa/Py + \text{intercept}$$

where, e is the porosity of the tablet, Pa the applied pressure and Py the heckel parameter (often referred to as the yield pressure). Heckel numbers, ln(1/e), were determined for ejected tablets (out-of-die procedure) prepared in a range of compaction pressures between 25 and 200 kg/cm2[17].

3.5.2 Particle size and morphology

Particle size and morphology of the co-processed excipient was determined by optical microscopy. A small quantity of excipient was placed on a clean glass slide. The slide was mounted on the stage of the microscope and diameter of 200-300 particles was measured using a calibrated ocular micrometer. The process was repeated for each batch[18][19].

3.5.3 Dilution potential

Maximum amount of drug which can be incorporated along with a fixed quantity of excipients to yield a tablet with acceptable hardness and friability is the dilution potential of the given excipient. The co-processed excipient in varying ratio is mixed with a fixed quantity of drug and lubricant and compressed over a rotary tablet compression machine to yield tablets which are then analysed for tensile strength and friability[20].

3.6 Preparation and evaluation of zaltoprofen tablets

The prepared co-processed excipient was mixed with 80 mg of zaltoprofen, disintegrating agent and lubricant. The mixture was directly compressed into tablets over a rotary tablet compression machine (Mini tab-1, Karnavati Engineering, India). The prepared tablets were subjected to following evaluation parameters[21].

3.6.1 Tensile strength

The dimensions of tablets were measured by using a vernier calliper. The crushing strength was determined after 24 hr (time for stress relaxation) of compression, by using a Monsanto hardness tester. From the values of diameter (D, cm), thickness (L, cm), and crushing strength (P, Kg), the tensile strength (T) (kg/cm2) of the tablets was calculated by using following equation[22].

$$T = 0.0624 * P / D * L$$

3.6.2 Friability

Roche friabilator was used for friability determination. The tablets equivalent to 6.5 g were taken and placed in friabilator. The friabilator was rotated at 25 rpm for 4 minutes. The tablets were then dedusted and weighed. Friabilty was calculated using the following formula[23].

$$\% \text{ Friability} = [(Wo - Wt)/Wo] \times 100$$

where, Wo is the initial weight of tablets and Wt is weight after friability test.

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3.6.3 Disintegration test

Disintegration test was performed for fast dissolving tablets using USP disintegration apparatus with phosphate buffer pH 6.8, 900ml at 37°C as the disintegration medium[24].

3.6.4 In vitro dissolution study

The dissolution study was performed using USP type II dissolution apparatus using phosphate buffer pH 6.8. The temperature was maintained at 37±0.5°C and speed of the paddles was set to 100 rpm. 5ml of aliquots were withdrawn periodically at 0, 10, 15, 20, 30, and 45 minutes and replaced with a fresh dissolution medium. Samples were filtered through a 0.45 micron membrane filter and concentration of zaltoprofen was determined using UV-Visible spectrophotometer at 338 nm[25].

4. Results

4.1 Evaluation and regression analysis of design batches

The design batches were evaluated for angle of repose, Carr's index, Hausner's ratio and percentage yield. The summary of results is presented in Table 2 and the results of statistical analysis of design batches is given in Table 3. All the readings were taken in triplicate and the average along with standard deviation is presented. It has been found that the independent variables have a significant effect on response variables ($p<0.05$).

Table 2: Summary of evaluation results for design batches

Run order	Batch	Angle of repose (Y1)	Carr's index (Y2)	Hausner's ratio (Y3)	Yield (%) (Y4)
1	C3	24.96± 0.08	9.31±0. 05	1.08±0. 06	45.21± 1.06
2	C4	26.43± 0.03	15.31± 0.08	1.10±0. 04	39.22± 1.08
3	C1	45.18± 0.07	23.42± 0.05	1.16±0. 04	29.14± 1.12
4	C6	34.50± 0.05	21.58± 0.04	1.14±0. 07	33.27± 1.14
5	C8	33.42± 0.08	20.31± 0.07	1.12±0. 04	34.22± 1.06
6	C2	27.37± 0.05	16.53± 0.05	1.18±0. 06	36.52± 1.21
7	C9	23.33± 0.05	9.74±0. 06	1.08±0. 05	46.24± 1.17
8	C5	25.92± 0.05	12.84± 0.07	1.09±0. 06	35.27± 1.15
9	C7	25.24± 0.05	12.82± 0.05	1.07±0. 08	37.28± 1.07

Regression analysis for different response variables was done and the polynomial equations generated are ($p<0.05$):

(Angle of repose) Y1 = 47.11 - 6.40 X1 (MC:MA) - 2.36 X2 (Inlet air temperature °C)

(Carr's index) Y2 = 28.97 - 5.16 X1 (MC:MA) - 1.44 X2 (Inlet air temperature °C)

(Hausner's ratio) Y3 = 1.18 - 0.0267 X1 (MC:MA) - 0.0067 X2 (Inlet air temperature °C)

(% Yield) Y4 = 22.66 + 5.673 X1 (MC:MA) + 1.682 X2 (Inlet air temperature °C)

The angle of repose values for the experimental design batches ranges between excellent to passable category as per USP i.e 23 to 45. It is evident from the equation Y1 that X1 and X2 terms have negative value which implies that as the MC:MA concentration and inlet temperature increases angle of repose decreases. The decrease in angle of repose is an indicative of improved flow property of prepared co-processed excipient. As the X1 term is higher than X2 in equation Y1 this suggests that MC:MA ratio has more significant impact on angle of repose as compared to inlet air temperature. As implicated from the contour plot shown in Figure 1(a) it can be inferred that as the MC:MA and air inlet temperature increases angle of repose decreases or flowability increases. The reason which may be attributed for this is that at higher inlet temperature there is swift evaporation of solvent resulting in free flowing dried powder particles. The value of Carr's index ranges between 9 to 23 which indicates passable to excellent compressibility. The value of Hausner's ratio ranges between 1.07 to 1.18 which confirms good to excellent flowability. The equations Y2 and Y3 both have negative X1 and X2 terms which perspicuously confirms the fact that MC:MA ratio and air inlet temperature have negative effect on both Carr's index and Hausner's ratio. The equation Y4 depicting yields value having positive value for terms X1 and X2 which lead to inference that increment in MC:MA ratio and inlet air temperature leads to increased yield of co-processed excipient[26][27].

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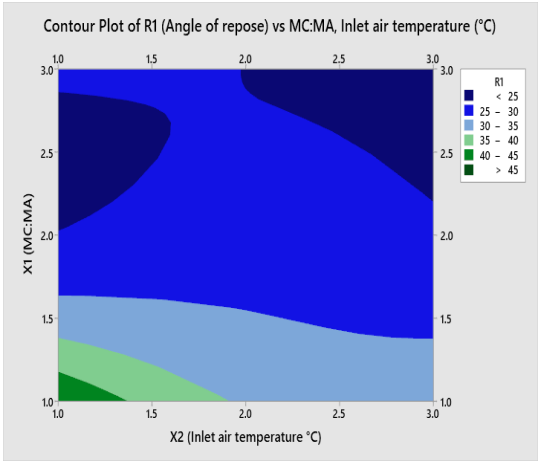
a.



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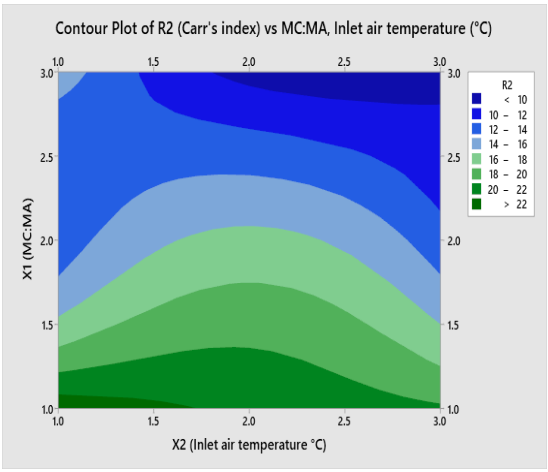

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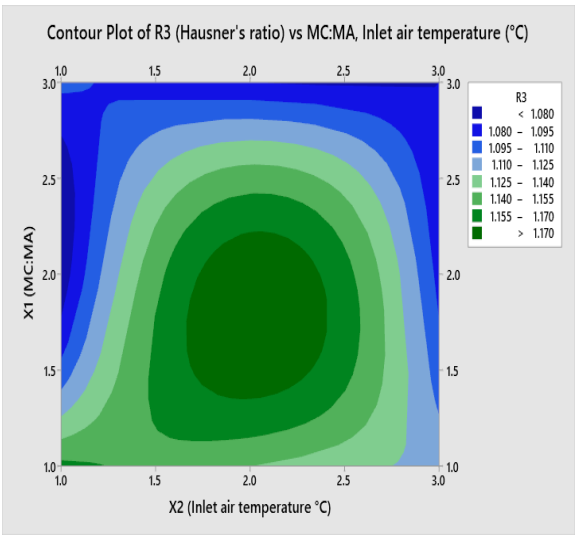

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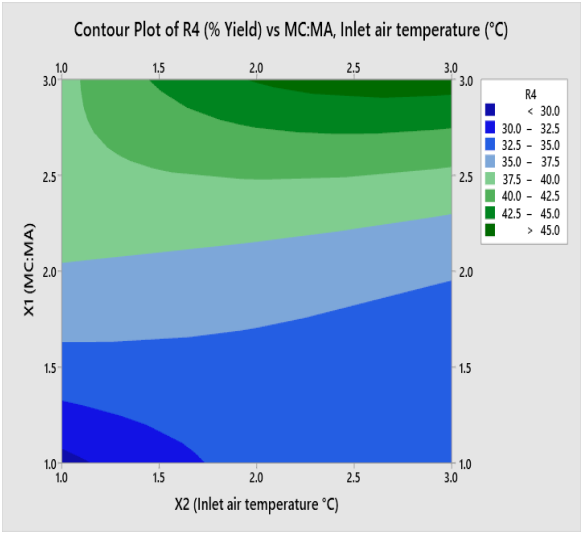

Figure 1 (a) Contour plot representing the effect of MC:MA and inlet air temperature on angle of repose. (b) Contour plot representing the effect of MC:MA and inlet air temperature on Carr's index. (c) Contour plot representing the effect of MC:MA and inlet air temperature on Hausner's ratio. (d) Contour plot representing the effect of MC:MA and inlet air temperature on % yield.

4.2 Response optimization for selection of optimized batch

The optimized batch was selected by optimizing the responses obtained as shown in Table 3. The goal was to minimize angle of repose, Carr's index, Hausner's ratio and to maximize percentage yield. The upper and lower limit is automatically selected by software on the basis of data assembled. The composite desirability value was found to be 0.9492.

Table 3: Response optimization for optimized batch selection

S. No.	Response	Goal	Lower	Target	Upper
1.	Angle of repose (R1)	Minimize	23.33	45.18	
2.	Carr's index (R2)	Minimize		9.31	23.42
3.	Hausner's ratio (R3	Minimize		1.07	1.18
4.	% Yield	Maximize	29.14	46.24	

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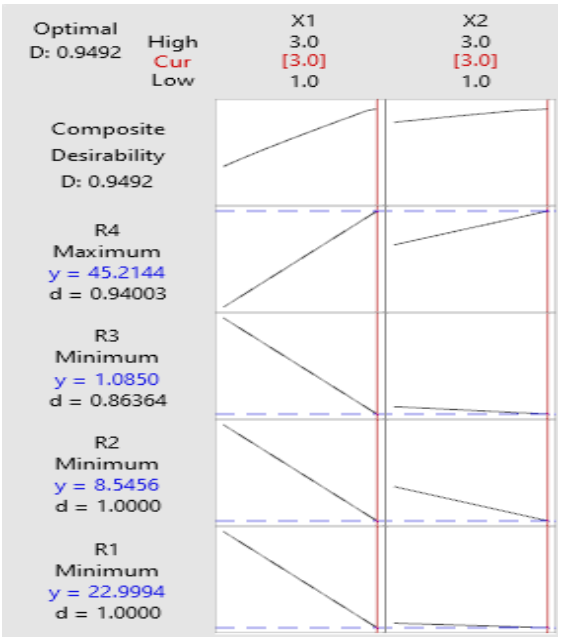

Figure 2: Response optimization plot for selection of optimized batch

4.3 Comparison between physical mixture and optimized co-processed excipient

A comparison between angle of repose, Carr's index and Hausner's ratio of physical mixture and co-processed excipient is presented in Figure 3.

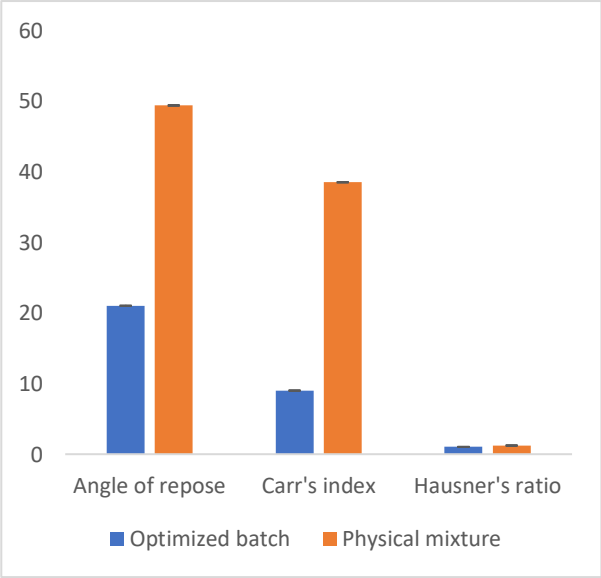

Figure 3: Comparison of physical properties of physical mixture and co-processed excipient

4.4 Characterization of optimized co-processed excipients

4.4.1 Heckel's plot

The compression behaviour of co-processed powder was analysed over a compression pressure of 50 to 200 kg/cm2. The yield value, Py value reflects the compression characteristics of the material; the lesser the value of Py, the greater is tendency towards plastic deformation. The yield value, Py was calculated by the value reflected by the slope of the regression line. The linear part of the curve represents the densification process indicating plastic deformation whereas elastic deformation is considered as negligible. The curved region of the plot represents the solitary movement of particles without any association. The shifting of curve to straight line represents the consolidation of particles into a compact mass; the point of transformation of curve to line represents minimum pressure required for consolidation[28]. The elastic deformation is found to be negligible. The values of yield pressure (Py) of different co-processed excipients is shown in Table 4 and Figure 4.

Table 4: Heckel plot parameters for different powder materials

S. No.	Powder type	Heckel's plot parameters	
		k	Py
1.	Optimized batch	0.60	82
2.	Physical mixture	0.42	85
3.	Mannitol	0.50	88
4.	MCC	0.44	89

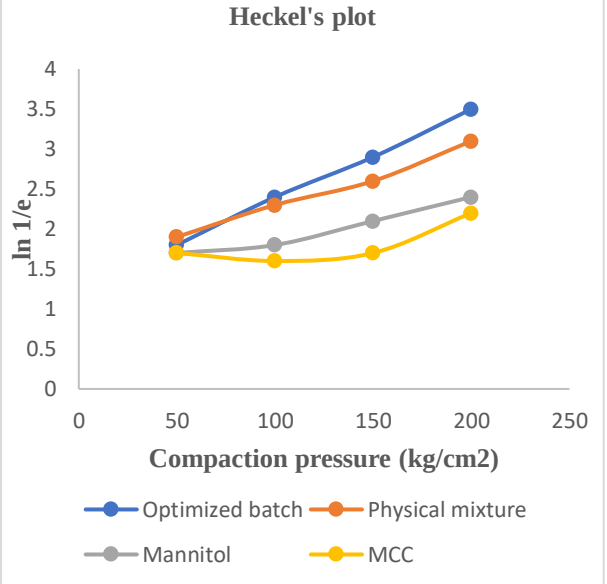

Figure 4: Heckel's plot for different powder types

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4.4.2 Particle size and morphology

The average particle size of spray dried co-processed excipient after excluding fines was found to be 212 ± 2.2 µm. The particle morphology of optimized batch as observed by optical microscopy is shown in Figure 5.

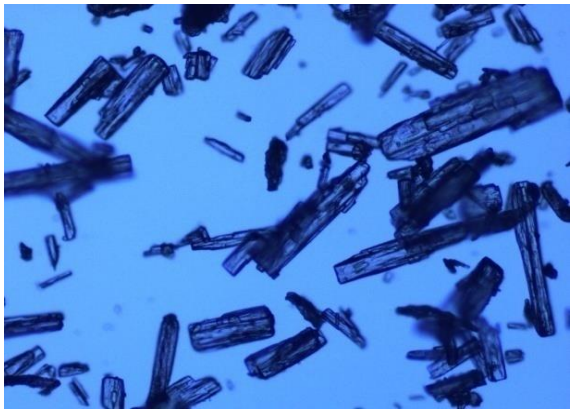

Figure 5: Optical micrographs of optimized batch of co-processed mannitol and MCC

4.4.3 Dilution potential

Different tablet batches using optimized co-processed excipients, for dilution study were prepared as shown in Table 5. The prepared batches were tested for tensile strength and friability. The results indicated that around 80% of drug can be mixed with co-processed excipient without losing its compressibility and any significant alteration in flow properties. Sodium starch glycolate was added to promote rapid disintegration.

Table 5: Composition for dilution potential study of co-processed mannitol and MCC

Ingredient	D1	D2	D3	D4	D5	D6
Optimized co-processed excipient (mg)	80	70	60	40	20	0
Zaltoprofen (mg)	20	30	40	60	80	100
Talc (mg)	4	4	4	4	4	4
Mg stearate (mg)	3	3	3	3	3	3
Sodium starch glycolate	3	3	3	3	3	3
Total weight (mg)	110	110	110	110	110	110

4.5 Preparation and evaluation of zaltoprofen tablets

4.5.1 Tensile strength

It was observed that as the dilution percentage increases tensile strength decreases as represented graphically in Figure 6.

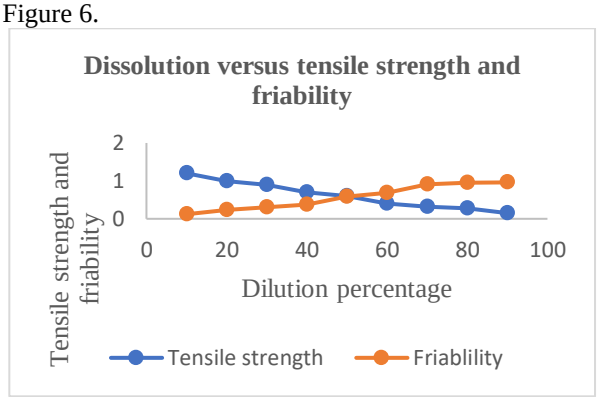

Figure 6: Diluent effect on friability and tensile strength

4.5.2 Friability

The percentage weight loss was less than 1% and no significant cracks or chipping has been observed. It has been observed that as the dilution potential increases friability increases as indicated in Figure 6. It has been found that up to 60% of dilution potential the friability is found within range, which clearly depicts that at least 40% of co-processed excipient must be present in the tablet to evade failure in friability test.

4.5.3 Disintegration time

The disintegration time for all the tested tablets is less than 8 minutes. This observation confirms the fast release of zaltoprofen from prepared tablets using developed co-processed excipient of MA and MCC.

4.5.4 *In vitro* dissolution study

Drug release from batches D1 to D3 was found to be 93%-95% within 25 minutes. For batch D4 containing around 36% of co-processed excipients the release was found to be up to 90% in a span of 30 minutes. The release from batch D5 is found to be 90% in 55 minutes which contains least amount of co-processed excipient.

5. Discussion

It has been found that MCC and MA when co-processed and optimized on the basis of various flow and compression properties lead to an excipient which is superior than physical mixture. It has been found that the optimized co-processed excipient when combined with model drug zaltoprofen leads to superior tablet properties as compared to physical mixture or MCC or MA alone. Thus present approach to develop an excipient with desired properties is achieved by co-processed MCC and MA excipient.

6. Conclusion

Optimized co-processed excipient of MC and MA has been prepared successfully by applying 32 full factorial

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design using spray drying process. The interaction between various factors has been explored by the design of experiment. The design of experiment approach revealed the effect of various input parameters on physical properties of co-processed excipient. It has been found that the optimized co-processed excipient has good flowability and compressibility. It is able to accommodate 80% of drug without any change in compressibility. Batch D2 was found to be optimized tablet batch. The tablets prepared by co-processed excipients were found to release 95% zaltoprofen within 25 minutes with a disintegration time of 8 minutes which fulfils the objective of fast release of zaltoprofen which is a poorly water soluble BCS Class II drug.

Conflicts of interest: None

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