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EFFECT OF MICROCRYSTALLINE CELLULOSE ON THE IMPROVEMENT OF MECHANICAL STRENGTH OF ORALLY DISINTEGRATING TABLETS USING CO-PROCESSED EXCIPIENT SYSTEMS

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ABSTRACT

Orally disintegrating tablets [ODTs] are oral solid dosage form which rapidly disintegrates or dissolves in mouth. A new coprocessed excipient system composed of mannitol, microcrystalline cellulose, Crospovidone and colloidal silicon dioxide was developed and evaluated to be used as diluent to improve mechanical strength and mouth feel of ODTs. This coprocessed excipient system can be used for taste masked and unmasked active pharmaceutical ingredients. The percentages of Mannitol, microcrystalline cellulose, Crospovidone, colloidal silicon dioxide were investigated by mixture design of response surface methodology. Different manufacturing process [Physical mixing, co-granulation (wet granulation)] were also evaluated. The results show that the mechanical strength and mouth feel are significantly improved with the optimized levels of coprocessed excipient composition. The optimized coprocessed excipient system with microcrystalline cellulose exhibited lesser weight variation during laboratory scale up. This four component coprocessed excipient system is homogeneously distributed and offers a readymade directly compressible diluent system for ODTs. This coprocessed excipient system is promising to keep ODTs affordable and patient friendly.

Key words: Orally Disintegrating Tablets [ODTs], Active Pharmaceutical Ingredient [API], Micro Crystalline Cellulose [MCC], Co-processing, Formulation, taste masking

1.0 INTRODUCTION:

Oral solid dosage forms are the most convenient and safe route among all other with the exception of children and elderly with dysphagia due to difficulty in swallowing. Tablets are most preferred dosage form by physician and pharmacist due to its dose accuracy and ease of administration also cost effectively manufactured. Clinically problem arises with swallowing difficulty and patient compliance. To ease the swallowing in oral route of administration orally disintegrating tablets [ODTs] dosage form was introduced in last decade across globe.

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USFDA defines ODTs "*A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue*"[1]. The ODTs are structured to disintegrate and possibly dissolve rapidly in mouth with presence of saliva eliminating the need of water and swallowing. Certainly ODTs are patient friendly drug delivery system to improve the compliance with the help of superior organoleptic properties such as taste, nongritiness and affordability. Commercial success of ODTs depends on superior palatability, stability across shelf life with least disintegration time, pharmacokinetic profiles and ease of manufacturing. The International Pharmaceutical Excipients Council (IPEC) defines excipient as "Substances, other than the API in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use" [2].

Excipients no longer maintain earlier perception of "inactive support" because they have influence on both biopharmaceutical aspects and manufacturing factors.[3] In order to deliver a stable, uniform and effective drug product, it is essential to know the properties of the active ingredient alone and in combination with all other ingredients based on the requirements of the dosage form and processes applied. There are three possible routes by which new excipients can be developed, (i) new chemical entities as excipients, (ii) new grades of existing excipients, and (iii) new combinations of existing excipients[4]. Creating a new chemical entity is expensive and lengthy to create all necessary toxicology and safety data[5]. Introducing new grades of existing excipient had been successful like pregelatinized starch, Croscarmellose sodium and crospovidone[6]. However finding a new excipient combination is a thirst area due to better and combined functionality and called as coprocessed excipient system. Co-processing is different excipients of functionality are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within granular agglomerates with a pre-defined particle size distribution. Segregation is diminished by adhesion of the actives on the porous particles making in-process control easy and reliable[7]. Coprocessing of excipients can be done by spray drying, wet or dry granulation, melt granulation, extrusion followed by spheronization, co-milling and co-crystallization. Spray drying is the method extensively investigated and proved successful[8]. Mannitol is widely used diluent for ODTs because it is porous, non-hygroscopic, highly compressible and offers cooling sensation and rapid disintegration in mouth. It occurs as a white, odorless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Granular mannitol flows well and imparts improved flow properties to other materials[9].

Lactose monohydrate as a natural disaccharide, obtained from milk, which consists of one galactose and one glucose moiety. Lactose is widely used as filler and diluent in oral solid dosage form includes tablets and capsules[10]. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently. A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products [11]. Active pharmaceutical ingredients and other excipients with primary amine group to be avoided with lactose monohydrate. Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes[12]. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[13] and disintegrant properties that make it useful in tableting. Crospovidone is a water-insoluble synthetic cross linked homo polymer of N-vinyl-2-pyrrolidinone. It is white to creamy-white, finely divided; free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder. Larger particles provide a faster disintegration than smaller particles. Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels[14]. Croscarmellose sodium is a cross linked polymer of carboxymethylcellulose sodium. Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets[15] and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. It rapidly swells to 4–8 times its original volume on contact with water and exhibits disintegration action. Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations [16]. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling[17]. Silicon dioxide, small particle size and large specific surface area give it desirable flow characteristics to flow properties of dry powders in tableting and capsule filling[18]. Set of coprocessing experiments were performed using physical mixing and wet granulation followed by fluid bed drying to screen the excipients suitability. Purified water was used as granulating fluid for wet granulation process. Coprocessed excipient systems suitably used as diluent in orally disintegrating tablets were prepared by co-granulation (wet granulation) in this study. A mixture design of surface response methodology was used to select the optimized composition which can be successfully laboratory scaled up.

2.0 MATERIALS AND METHODS:

2.1 MATERIALS:

Mannitol (Mannitol 25, extra fine crystalline Mannitol with mean diameter of 25 µ, Roquette), Lactose monohydrate [Pharmatose 200M, DFE Pharma), Crospovidone [Polyplasdone XL 10, ISP), Micro crystalline cellulose [Avicel PH105, mean diameter 20 µ, FMC bio polymer], Croscarmellose sodium [Ac-Di-Sol, FMC BIO

Polymer], Sodium Starch glycollate [Primojel, DFE Pharma], Colloidal silicon dioxide [Syloid 244FP, Grace division], Peppermint flavor [Firmenich flavors] Magnesium stearate [Ferro Pfanstiehl Laboratories Inc.] were used as supplied.

2.2 EXPERIMENT DESIGN

In pharmaceutical formulations, the 'one variable at a time method' requires many experiments and there is no assurance that an optimal formulation can be attained. Moreover, the interaction between different factors, which can impact the target responses, may not be detected. The use of an experimental design can be helpful in the optimization of pharmaceutical formulations[19]. A mixture design is a special type of response surface experiment in which the factors are the components of a mixture and the response is a function of the proportions of each component[20]. This method is dependent on predetermined statistical significance levels which mean less significant terms are not included in the models [21]. The response surface methodology (RSM) was applied for optimization of the study formulations. The optimized formulation was obtained from combined contour plot.

2.3 SELECTION OF EXCIPIENTS FOR CO-PROCESSING

The suitable excipients were selected by considering the functionality of material (Diluent, super disintegrant, glidant and lubricant) to balance the quality and robustness of the tablets. The selected excipients were blended with different proportions and co-processed for better mouth feel and mechanical strength. To screen the co-processed excipient mixture, tablets were compressed with sweetener and lubricant and evaluated for disintegration time, friability and mouthfeel.

2.4 PREPARATION OF COPROCESSED EXCIPIENT SYSTEM BY CO-GRANULATION

Co-granulation [wet granulation] refers to the act or process in which primary powder particles are made to adhere to form larger, multi particle entities called granules with the presence of liquid binder. Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties of blend. Purified water was used for wet granulation. The granulated mass was dried using fluid bed dryer and passed through #30 sieves to obtain granules. Direct physical mixing of final optimized formula also done to compare with wet granulated coprocessed excipient system. Mannitol, Lactose monohydrate and microcrystalline cellulose [MCC] were screened for diluents. Since MCC is insoluble in nature, higher quantity will result in the grittiness. To avoid grittiness of mouth feel microcrystalline cellulose was included in lesser amount to study the impact on ODT characteristics. Experiments were conducted with one thousand tablets batch size and compressed using 10mm diameter with flat faced and bevel edged tooling.

Base experiments were conducted and evaluated for bulk, tapped density, compressibility index, angle of repose (Blend) , friability and disintegration time (Tablets)

2.5 CHARACTERIZATION OF COPROCESSED EXCIPIENT SYSTEM:

2.5.1 Loss on drying:

Loss on drying was determined by moisture analyzer (Sartorius, Germany) heating mechanism through infra-red. About 1 g of each testing sample was distributed into a tray and the result was recorded until a constant reading was achieved.

2.5.2 Bulk density:

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. The bulk density of a powder is the weight of the powder divided by the volume it occupies, normally expressed as g/ml. The blend was passed through sieve #18 and weighed blend carefully levelled in measuring cylinder, unsettled apparent volume measured with nearest graduated unit.

2.5.3 Tapped density:

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample.

2.5.4 Compressibility (Carr's) Index & Hausner ratio:

Percent compressibility of powder mix was determined by Carr's compressibility index calculated by following formula.

Compressibility Index = (Tapped density−Bulk density) / Tapped density ×100

Hausner's ratio: The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by the ratio of tapped density and bulk density.

Hausner′s ratio =Tapped density/Bulk density

2.5.5 Angle of repose (Θ):

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

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

$\Theta = \tan^{-1}(h/r)$,

Θ is the angle of repose; h is the height; r is the radius. The granules were allowed to flow through the funnel fixed to a stand at definite height and Angle of repose was evaluated.

2.5.6 Tablet hardness:

The hardness was examined by using Hardness tester [Agilent 200 hardness tester]. The mean was calculated from three determinations.

2.5.7 Percent Friability

Friability was evaluated from the percentage weight loss of 20 tablets or equivalent to 6 gm tumbled in a friabilator (Electro lab, model EF2) at 25 rpm for 4 minutes. The tablets were dusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss.

2.5.8 Disintegration time

The disintegration time of tablet was measured in water (37^0 c) according to USP disintegration test apparatus.

2.5.9 Laboratory scales up:

The selected optimized composition of coprocessed excipient system was taken for laboratory scale up. In addition peppermint flavor (3mg), Sucralose (5mg) and magnesium stearate (3mg) per tablet were blended. The batch size of the experiment is 900gms [3000 Tablets]. All the ingredients were blended in double cone blender for 10 minutes at 15 rpm. Tablets were compressed using 16 station cadmach tablet compression machine using 10 mm flat faced and bevel edged tooling. The tablets were evaluated for weight variation, hardness, and friability and disintegration time at initial, middle and final stages of compression. Evaluation also done with two different compression machine revolutions [10 & 20 rpm].

3. RESULTS AND DISCUSSION:

3.1. Investigation of coprocessed excipient system by mixture design

The composition with Mannitol, Crospovidone, colloidal silicon dioxide and microcrystalline cellulose is taken for optimization with the application of Design of Experiments [DoE]. To predict the design space of following excipients at different levels (%w/w) and desired responses were considered. As per the Software's Experimental Design, 22 DoE Trials were carried out by keeping the experimental condition constant. Placebo tablets were compressed with consistent extra granular components and evaluated for disintegration time [DT] and Friability as responses. Disintegration Time of design of experiment trials was in the range of 8 to 24 sec, also a broad range suitable to optimize with the application of DoE. Friability of DoE trials was in the range of 0.14 to 1.46 %w/w, is a narrow range which is difficult to optimize as model didn't fit. The Model F-value of 80.91 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob>F" less than 0.0500 indicate model terms are significant. In this case X1X2, X2X4, X1X2X3 are significant model terms. Values of "Prob>F" greater than 0.1000 indicate the model terms are not significant. In this case Lack of fit model is not significant. ANOVA suggests that selected model is appropriate for Statistical Optimization. Contour plot was utilized to optimize the coprocessed composition graphically .The middle portion of the plots should be considered to optimize the composition with desired responses. Statistical data supports the selection. The selected Mixer design model is stable and robust enough to optimize the composition of co-processed excipient for desired disintegration time. Design of Experiments has given wide range of composition of the co-Processed Excipient for the desired disintegration time. Out of these various compositions best composition was selected by the middle point at desired region of plot. The optimized composition results in shorter disintegration time and less friability.

3.2 Coprocessed excipient system properties:

Initial experimentation for selection of diluent shows that the mannitol offers cooling sensation in mouth, better flow with quick disintegration time and mechanical strength while comparison with lactose monohydrate. Out of three super disintegrants, crospovidone provided lesser disintegration time. Inclusion of microcrystalline cellulose and silicone dioxide contributed in necessary hardness with rapid disintegration of orally disintegrating tablets. It is often difficult to find a balance between hardness and disintegration. However this co-processed excipient system which is composed of four component system exhibited superior properties than the physical mixture of individual components also balances the disintegration and hardness [lesser friable]. The lower angle of repose indicates that co-processed excipient system exhibit better flow which results in lesser weight variation and there by better uniformity of dosage unit. The mixture design of response surface methodology was successfully used to optimize composition of this four component co-processed excipient system suitable to be used as diluent in directly compressible orally disintegrating tablets.

3.3 Orally disintegrating tablet Properties:

Combined contour plot shows that the each component of coprocessed excipient system has great influence on disintegration time of ODTs. Increase in Crospovidone concentration decreased disintegration time and resulted more friable. Higher concentration of microcrystalline cellulose improved mechanical strength of tablets and less friable. Higher concentration of silicon dioxide resulted in increase of tablet friability this may be due to porous nature and air entrapment in compressed tablets. The observed moisture content was not more than 2.0 %, the performance of ODT s may hinder due to the presence of excessive moisture. So it is recommended for co-processed excipient system and compressed tablets to be protected from moisture pick up. The comparison between the four

component co-processed excipient system with physical mixing of optimized formula showed the presence of capping during friability and disintegration testing when the excipients are just physically mixed. The observed disintegration time of optimized composition of orally disintegrating tablet is not more than 15 seconds which is less than 30 seconds requirement of USFDA guideline for 500 mg tablet.

Table 1: Formulation Composition

Ingredients	Quantity in mg				
	Category	F1	F2	F3	F4
Intra granular					
Mannitol	Diluent	257.5	257.5	--	242.5
Lactose monohydrate	Diluent	--	--	257.5	--
Microcrystalline cellulose	Diluent	--	--	--	15.0
Croscarmellose sodium	Super disintegrant	22.5	--	--	--
Sodium starch glycolate	Super disintegrant	--	22.5	--	--
Crospovidone	Super disintegrant	--	--	22.5	22.5
Silicon dioxide	Glidant	9.0	9.0	9.0	9.0
Purified water	Granulating fluid	q.s	q.s	q.s	q.s
Extra granular					
Peppermint flavor	Flavor	3.0	3.0	3.0	3.0
Sucralose	Sweetener	5.0	5.0	5.0	5.0
Magnesium stearate	Lubricant	3.0	3.0	3.0	3.0
Total weight (mg)		300.0	300.0	300.0	300.0
Observation : Blend characterization					
Angle of repose		32.2	34.6	31.8	24.2
Bulk density (gm/ml)		0.47	0.50	0.45	0.42
Tapped density (gm/ml)		0.62	0.70	0.59	0.53
Compressibility index (%)		23.8	22.4	23.9	20.8
Hausner ratio		1.31	1.40	1.32	1.26
Moisture content (LOD - %)		2.10	1.75	1.82	1.65
Compression parameters					
Disintegration time [Sec}		16 to 19	14 to 17	12 to 14	10-13
Friability (%w/w)		0.8	0.9	0.7	0.5
Hardness (kp)		5-7	5-7	5-7	5-7
Thickness (mm)		3.22-3.26	3.22-3.27	3.22-3.25	3.13-3.22
Average Weight (mg) [Target: 300 mg]		304	300	303	304

Table 2: Variables and responses of experimental design

Independent Variables	Range [mg]	Responses
X1- Quantity of Mannitol	210-270	1. Disintegration time 2. Friability
X2- Quantity of Crospovidone	12-45	
X3- Quantity of Microcrystalline cellulose	6-30	
X4- Quantity of Silicon dioxide	3-15	

Table 3. Design summary [Design Expert (8.0.2 version software)]

Study Type	Mixture	Runs	22
Design Type	IV-optimal	Blocks	No Blocks
Design Model	Quadratic	Build Time (ms)	635.59

Table 4. Factor details of Intra granular optimization

Component	Name	Units	Min.	Max.	Low Actual	High Actual	Std. Dev.
X1	Quantity of Mannitol	mg	208.1	260.1	202.3	260.1	5.19
X2	Quantity of Crospovidone	mg	11.6	43.4	11.6	43.4	4.28
X3	Quantity of Microcrystalline cellulose [MCC]	mg	5.8	28.9	5.8	28.9	3.25
X4	Quantity of Silicon dioxide	mg	2.9	14.5	2.9	14.5	1.66

Table 5. Design of experiment trials

RUN	Component X1	Component X2	Component X3	Component X4	Response 1	Response 2
	Mannitol	Crospovidone	MCC	Silicon dioxide	Disintegration time	Friability
1	218.2	27.4	28.9	14.5	11	0.46
2	224.6	32.7	28.9	2.9	12	0.23
3	221.7	43.4	21.1	2.9	9	0.22
4	258.1	11.6	5.8	13.6	16	0.58
5	213.9	43.4	17.3	14.5	11	0.14
6	241.9	11.6	28.9	6.7	21	0.30
7	236.1	32.7	5.8	14.5	12	0.81
8	239.6	25.2	15.9	8.4	14	0.31
9	241.9	11.6	21.1	14.5	15	0.93
10	218.2	27.5	28.9	14.5	12	0.48
11	252.3	25.1	5.8	5.8	17	0.32
12	237	43.4	5.8	2.9	10	0.27
13	260.1	11.6	14.6	2.9	24	0.50
14	239.6	25.2	15.9	8.4	14	0.30
15	208.1	43.4	28.9	8.7	10	0.26
16	234.9	22.3	28.9	2.9	16	0.24
17	225.4	43.4	5.8	14.5	8	1.46
18	237.0	43.4	5.8	2.9	10	0.23
19	258.1	11.6	5.8	13.6	18	0.57
20	241.9	11.6	28.9	6.7	20	0.42
21	260.1	11.6	14.5	2.9	24	0.50
22	228.6	26.3	22.6	11.6	11	0.36

Table 6. Response summary

Response	Name	Units	No of trials	Analysis	Min.	Max.	Mean	Std. Dev.	Model
1	Disintegration time	seconds	22	Polynomial	8	24	14.31	4.79	Quadratic
2	Friability	% w/w	22	Polynomial	0.14	1.46	0.45	0.31	RCubic

Table 7. ANOVA of Models

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Remark
Model	453.56	7	64.8	80.91	< 0.0001	Significant
Linear Mixture	395.01	3	131.7	164.43	< 0.0001	
X1X2	8.13	1	8.1	10.15	0.0066	
X2X4	27.17	1	27.2	33.92	< 0.0001	
X3X4	2.88	1	2.9	3.59	0.0789	
X1X2X3	3.64	1	3.6	4.55	0.0512	
Residual	11.21	14	0.8			
Lack of Fit	8.71	8	1.1	2.614	0.1291	Not significant
Pure Error	2.50	6	0.4			
Total	464.77	21				

Table 8 .Optimized coprocessed excipient system composition for ODTs

S.No	Ingredients	% composition	mg / Tablet
Intragranular			
1	Mannitol	78	234.0
2	Microcrystalline cellulose	6	18.0
3	Crospovidone	9	27.0
4	Silicon dioxide	3	9.0
5	Purified water	qs	qs
Extragranular			
6	Peppermint flavor	1	3.0
7	Sucralose	2	6.0
8	Magnesium stearate	1	3.0

Table 9. Blend and compression characterization comparison:

Parameter	Observation	
	Physical mixing	Cogranulation
Blend characterization		
Angle of repose	34.6	24.2
Bulk density (gm/ml)	0.39	0.44
Tapped density (gm/ml)	0.74	0.56
Compressibility index (%)	47.00	20.99
Hausner ratio	1.80	1.27
Moisture content (LOD)	1.45	1.65
Compression observation		
Disintegration time	10-12 / two layers formed	12-14
Friability (%w/w)	Capping observed	0.33
Hardness (kp)	5-7	5-7
Thickness (mm)	3.10-3.20	3.20 -3.30
Average Weight (mg) [Target: 300 mg]	302.0	304.0

Table 10. Laboratory scale up – characterization [Tablet press revolutions -10 rpm]

Initial	Weight of tablet	Middle	Weight of tablet	Final	Weight of tablet
1	304.2	11	295.3	21	292.4
2	299	12	298.3	22	299.7
3	303.2	13	300.4	23	306.4
4	306.4	14	292.4	24	307.2
5	304.2	15	290.2	25	305.2
6	308.2	16	301.8	26	300.2
7	306.2	17	306.7	27	307.2
8	301.8	18	304.7	28	304.8
9	294.4	19	308.1	29	306.9
10	297.2	20	304.7	30	302.5
Observation					
Average weight		302.0			
Min		290.2			
Max		308.2			
SD		5.12			
%RSD		1.69			
Disintegration time		12-14 seconds			
Hardness [kp]		5-7 kp			
Friability [%w/w]		0.35			

Table 11. Laboratory scale up – characterization [Tablet press revolutions -20 rpm]

Initial	Weight of tablet	Middle	Weight of tablet	Final	Weight of tablet
1	299.6	11	296.3	21	304.2
2	301.5	12	299.1	22	305.2
3	300.3	13	293.3	23	299.7
4	294	14	303.3	24	302.4
5	296.4	15	304.2	25	301.4
6	304.3	16	301.1	26	302.3
7	302.1	17	300.4	27	305.6
8	296.3	18	306.7	28	308.3
9	301.4	19	308.3	29	302.1
10	293.8	20	301.1	30	304.2
Observation					
Average weight		301.3			
Min		293.3			
Max		308.3			
SD		3.99			
%RSD		1.33			
Disintegration time		13-15 seconds			
Hardness [kp]		5-7 kp			
Friability [%w/w]		0.33			

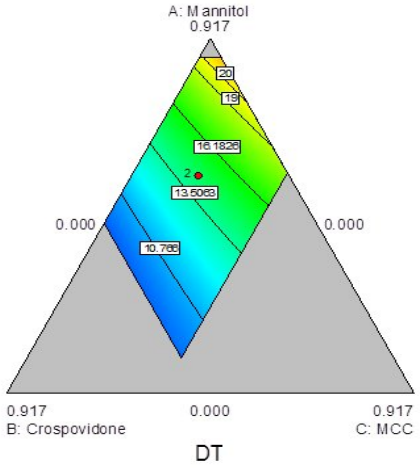

Figure 1: Contour plot

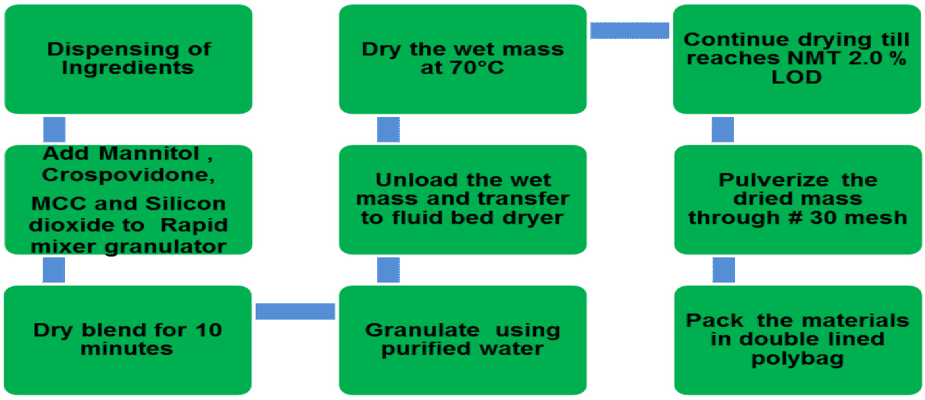

Figure: 2: Manufacturing Process – Flow chart

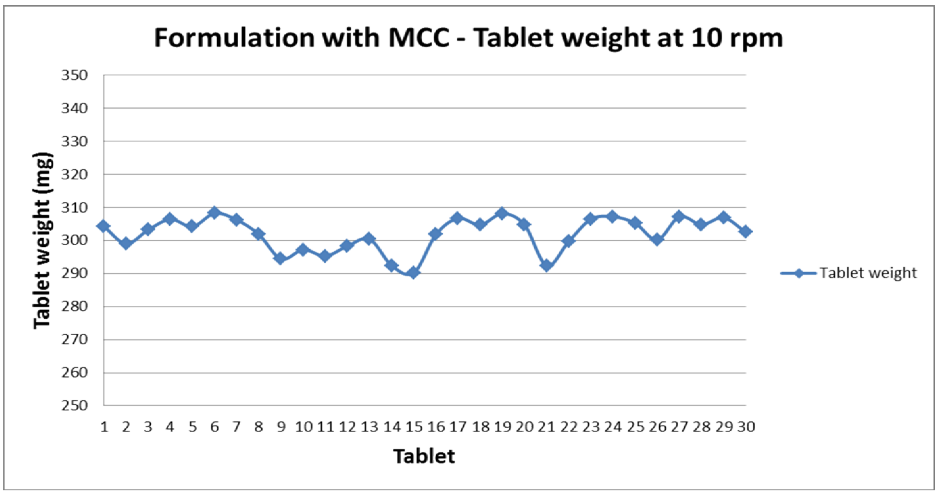

Figure 3. Weight variation observed at 10 rpm

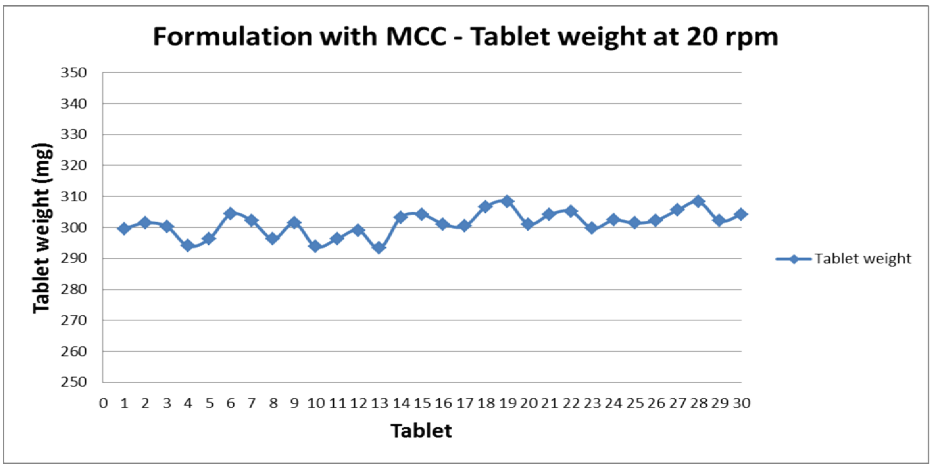

Figure 4. Weight variation observed at 20 rpm

4.0 CONCLUSION

New coprocessed excipient system consisting of Mannitol, Microcrystalline cellulose, Crospovidone and Silicon dioxide was developed to be used as diluent in orally disintegrating tablets in this investigation. The factors affecting the properties of the coprocessed excipient system were evaluated by mixture design of response surface methodology. The results showed that the mechanical strength of orally disintegrating tablets significantly improved with increasing percentage of microcrystalline cellulose and without compromising disintegration ability. Compared to physical mixing the developed coprocessed excipient system by co-granulation [wet granulation] have better flow, less weight variation without capping during tablet compression. The improvements are mainly attributed by the addition of microcrystalline cellulose in the coprocessed excipient system. The optimization of composition was located using statistical fitted models and the contour plot of disintegration time response. The statistical mixture design has the advantage of performing a small number of experiments and the fitted model from the statistical analysis can be used to predict values of responses at any point inside the experimental space. The mixture design can be successfully used to optimize the composition of coprocessed excipient system which can be used as diluent in orally disintegrating tablets. The evaluation of the laboratory scale-up of optimized coprocessed excipient system with flavor, sweetener and lubricant showed that the blend had acceptable flow properties. The laboratory scale-up tablets were evaluated and their tablet properties were acceptable. The developed four component coprocessed excipient system is promising and considered for further development. The statistical mixture design is a powerful tool to optimize formulation with a reproducibility of product characteristics.

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