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Research Article

Development and Evaluation of Co-Processed Excipient for Orally Dissolving Tablets

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ABSTRACT

In this study, attempts were made on the design, development and evaluation of co-processed excipient that would be helpful in preparing Orally Dissolving Tablet. Co-processed excipient is mainly composed of known additives that are commonly used in the manufacturing of ODTs including mannitol, Microcrystalline Cellulose (MCC) and maize starch. Among different available techniques for co-processing, a more economical conventional technique was selected for the developing co-processed excipient consisting of excipient sizing, blending and physical agglomeration by wetting, wet screening, drying and followed by dry screening.

Experiments were performed according to 32-level factorial design to observe the effect of two variables on critical quality attributes of co-processed excipient. The concentration of Microcrystalline Cellulose (X1) and maize starch (X2) were two numeric factors (independent variables). The studied responses were critical quality attributes of co-processed excipient.

All possible nine combinations were prepared and F4 formulation was selected as optimized based on its quality parameters. Later it was used with low content API (Active Pharmaceutical Ingredient) Montelukast sodium and high content API Paracetamol taste masked granules to prepare Orally Dissolving Tablet and each was evaluated for all critical quality attributes.

It is concluded co-processed excipient developed in the current study is cost effective, reproducing and meeting all quality criteria for further developing Orally Dissolving Tablet.

Keywords: Orally Dissolving Tablets (ODTs), Co-processed excipients, Mannitol, microcrystalline cellulose, Maize starch, Factorial design

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INTRODUCTION

From the last three decades, the transformation of technology in the field of pharmaceutical manufacturing towards the development of patient centered dosage form lead the formulation scientist to develop different types of dosage form, among them Orally Dissolving Tablet (ODTs) is an emerging field and key area of research. ODTs are like other conventional tablets but are formulated with those excipients that can easily dissolve in mouth with the help of saliva without using water (Nagar P, *et al.*, 2011). ODTs were originally developed to avoid swallowing problems of tablets and capsules in different age groups specially pediatric and geriatric patients. Different methods are reported in literature for the manufacturing of ODTs but are not limited to like sublimation, molding, lyophilization or freeze drying, mass extrusion, melt granulation and direct compression. By design, disintegrating property of ODTs in mouth without the use of water is because of the emerging technology of co processing of different excipients to produce a single excipient with multifunctional properties that are not present in the simple physical mixture of the component excipients (Amelian A, *et al.*, 2016). Co processing of excipients modify the physical blend of individual materials without any chemical alteration in the structure and has number of benefits like improve flow properties, compressibility, better dilution potential, decrease lubricant sensitivity plus selection of wide range of plastic and brittle materials that prevent the storage of elastic energy during compression and reducing the strength of capping and lamination (Bowles BJ, *et al.*, 2018). Formulation scientist in the recent years have recognized that there is no single excipient that can full fill the criteria require for ODTs there for new method called co processing of existing excipient is introduced to develop a single excipient that can full fill the requirement like rapid disintegration and good mouth feel of ODTs. Some commercially available co processed excipients are pearlitol flash, ludiflash, prosolv ODT G2, pharmburst and parteck. Different methods are available for the development of co processing like spray drying, solvent evaporation, crystallization, melt extrusion and wet granulation.

In the present study wet granulation method is used to develop co-processed excipient from already available excipients which were selected based on their physicochemical properties, safe use in oral medication, and functional role in Orally Dissolving Tablet. Critical quality attributes of each ingredient was also considered before using in the formulation development. Quantity of each ingredient was selected through design of experiment followed by manufacturing of initial batches and evaluation their physicochemical parameter for the selection of most suitable formulation for preparing Orally Dissolving Tablet dosage form with low and high drug content.

MATERIALS AND METHODS

Materials

Paracetamol taste masked granules was obtained from Surge Laboratories. Montelukast sodium was arranged from Zhejiang Tianyu Pharmaceutical. Mannitol was obtained from Qingdao Bringhtmoon Seaweed. Microcrystalline Cellulose PH 102 from Reliance Cellulose Products Ltd, maize starch from Rafhan maize Products Co Ltd, Sucralose from JK Sucralose Inc and sodium stearyl fumarate from Standard Chem and Pharma Co. Coloring and Flavoring agents were obtained as gift from Bush Boake Allen Inc and Givaudan respectively.

Methods

Design of experiment: Co-processed granules were developed for Orally Dissolving Tablet with the help of systematic formulation approach. Experiments were performed according to 3-level factorial design to study the effect of two formulation variables on critical quality attributes of Orally Dissolv-

ing Tablet. The concentration of Microcrystalline Cellulose (X1) and maize starch (X2) were two numeric factors (independent variables). The studied responses were critical quality attributes of Orally Dissolving Tablet including hardness, disintegrating time and wicking time (dependent variable). All nine possible experimental trials were performed. Independent and dependent variables along with their levels, qualitative composition and matrix of the factorial design were prepared accordingly.

Preparation of co-processed excipient: Quantitative composition of all formulations from F1 to F9 were prepared. Mannitol, Microcrystalline Cellulose PH 102 and maize starch were taken after weighing exact quantities according to specific formulation code. All ingredients were passed through sieve #40 mesh to break any lumps and mix well for 10 minutes to produce uniform blend. Wet granulate the powder blend with purified water and kneed well to get uniform wet mass. Damp mass was passed through sieve #10 mesh and spread the wet granules on a tray for drying at temperature 50°C. Drying process was continued till moisture content reached at less than 2% followed by the dried granules were passed through sieve #30 mesh and collected in polybag.

Evaluation of co-processed excipient

Appearance: Appearance of granules was inspected visually by spreading on a petri dish. Appearance described by estimating fines and granular material in a sample along with color of granules ranged from white to off-white.

Moisture determination: The moisture of all specimens were measured by moisture balance. 1.0 gm sample of granules of each formulation was positioned inside the drying chamber in small hot plate to heat the sample; temperature was set at 105°C and started until the weight was constant. Each sample was examined in triplicate and the result obtained as the arithmetic average on all the determinations.

Granules friability test (by oscillating apparatus): Remove the particles by sieving (sieve having an aperture size of 250 µm). In the glass container, weigh about 10.0 gm of the granules. Install the container in the apparatus. Shake for 120 s at a frequency 140 oscillations/min. Sieve through 250 µm and weigh the granules. Calculate granules friability as percentage weight loss.

Bulk Density(BD) and Tapped Density(TD): A known mass of powder is added to a graduated cylindrical to calculate the Bulk Density. The density is measured in terms of mass/volume (gm/ml). The Bulk Density relies on both the powder composition of the particles and how the powder particles are distributed.

The Tapped Density is obtained by taping a graduated tube that holds the sample mechanically until a small change of volume has been detected. The Tapped Density is measured as a weight divided by the final powder volume.

Hausner ratio/Carr's index: The Hausner ratio is a percentage associated with a powder or granular material's flow ability. It is named for Henry H. Hausner (1900-1995) the scientist. The Hausner ratio is defined by the equation

H=Tapped Density (TD)/Bulk Density (BD)

Where BD is the powder's loosely settled Bulk Density and TD is the powder's tapped Bulk Density. The Hausner ratio is not a material's complete property; its meaning can vary depending on the methods used to calculate it.

An indication of the compressibility of a powder is the Carr's index or Carr's compressibility index. It is named for Ralph J. Carr, Jr., a physicist. The equation used to measure the Carr's index.

C=100 (VT-VB/VT)

Where VB is the volume that would occupy a given mass of powder if it were allowed to settle freely, and VT is the volume that would occupy the same mass of powder after tapping down. It may also be expressed as C=100 (1-BD/TD). Where BD is the powder's freely settled Bulk Density and TD is the powder's tapped Bulk Density

Angle of repose: It was calculated to shape a cone by pouring the powder into the funnel. To minimize the impact of dropping particles the tip of the funnel was kept closed to the rising cone and lifted gradually as the pile rises. The material is poured through a funnel to form a cone. The samples were graded as per scale of flowability, Angle of Repose=Tan-1 Ø (2h/d) (Gohel *et al.*, 2003) (Singh and Kumar, 2012) *(Table 1)*.

Particle size distribution: Each sieve was weighed, assembled in an ascending order #40 mesh, #60 mesh, #80 mesh and #100 mesh and placed the pan below sieve #100 mesh. 50 gm sample was taken into top sieve and placed the cap over it. Sieve stack was placed in the mechanical shaker and run for 10 minutes. Sieve stack was removed from shaker, weighed and weight of each sieve was recorded. The results were calculated as %age retained on each sieve.

Post-compression parameters

Weight uniformity test: Individually 20 units selected at random, weighed and average weight was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage limit and none deviates by more than twice of that percentage.

Hardness: Hardness is the tensile strength of the tablets and is measured in terms of load /pressure that is required to crush it when placed on its edge. Disintegration and dissolution are affected by hardness of the tablet, which in turn affect the bioavailability. Monsanto hardness tester is used for the measurement of hardness of the formulated tablets. It is expressed in kg/cm^3.

Friability: Friability of the tablets was calculated from percentage weight loss of 20 tablets that are tumbled in a Friabilator at 25 ± 1 rpm for 100 rpm. These tablets were then de-dusted, and the loss in weight caused by fracture loss or abrasion was noted as percentage weight loss for friability.

Wetting time and water absorption ratio: Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and DT. To illustrate wetting of the tablet, a piece of tissue paper folded twice was placed in a petridish (internal diameter 6.7 cm) with 10 ml of water containing a water-soluble dye. A tablet was carefully placed on the surface of tissue paper and the time required for water to reach upper surface of tablet was noted as wetting time that indicates complete wetting of tablets. The ratio of water absorption is calculated by the difference between tablet weight before absorption and tablet weight after absorption.

$R=\{(Wa-Wb)/Wb\} \times 100$

Disintegration time: The DT was measured using a modified disintegration method (n=5). For this purpose, a petridish (6.5 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the petridish and the time for the tablet to completely disintegrate into fine particles was noted (Gohel M, *et al.*, 2004).

***In-vitro* dispersion time:** In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated salivary fluid (Phosphate buffer PH 6.8) to ensure disintegration of tab-

lets in the salivary fluid (Venkatesh DP and Rao CG, 2014).

Tablet with low content of API and high content API: After getting optimized formulation from above experiments, granules of optimized formulation was taken to prepare tablet dosage form with low content of API. Montelukast sodium was chosen for said purpose and Montelukast sodium Tablet 5 mg was prepared containing above co-processed excipients along with sweetening agent, flavoring agent and lubricant.

Paracetamol was chosen for preparing orodispersible tablet as high drug content. Granules of optimized formulation was mixed with Paracetamol taste masked granules to prepared Paracetamol orodispersible tablet 125 mg and for patient compliance some adjuvants were also added including sweetening agent and flavoring agent. The tablets containing different drug: excipients blend ratios were evaluated for drug content, weight variation, hardness, friability, angle of repose and DT (Gohel M, *et al*., 2004).

RESULTS AND DISCUSSION

Orally Dissolving Tablet is more palatable and drug availability is quite faster than other immediate release tablet dosage form. Patience compliance is also excellent for pediatric and geriatric class and also in the patients where the fear of swallowing a tablet is very high. In parallel to its merits there are many challenges to develop such dosage form for high drug content medication and also for those which are bitter in taste. However different measures can be taken to cope with such challenges and making a stable system for developing Orally Dissolving Tablet dosage form.

In current study, attempts were made on the design, development and evaluation of co-processed excipients that would be helpful in preparing Orally Dissolving Tablet. Co-processed excipient is mainly composed of known pharmaceutical additives that are commonly used in the manufacturing of ODTs including mannitol, Microcrystalline Cellulose and starch along with some adjuvants like lubricant, flavoring agent and sweeteners for patient compliance.

Co-processed granules were developed for Orally Dissolving Tablet with the help of systematic formulation approach. Experiments were performed according to 3-level factorial design to study the effect of two formulation variables on critical quality attributes of Orally Dissolving Tablet.

The concentration of Microcrystalline Cellulose (X1) and maize starch (X2) were two numeric factors (independent variables). The studied response were critical quality attributes of Orally Dissolving Tablet including hardness, disintegrating time and wicking time (dependent variable). All nine possible experimental trials were performed. Independent and dependent variables along with their levels, qualitative composition and matrix of the factorial design were presented in *Tables 1-3*.

Table 1: Scale of flowability

Compressibility index (%)	Flow character	Hausner ratio	Angle of repose (degrees)
≤ 10	Excellent	1.00-1.11	25-30
Nov-15	Good	1.12-1.18	31-35
16-20	Fair	1.19-1.25	36-40
21-25	Passable	1.26-1.34	41-45
26-31	Poor	1.35-1.45	46-55
32-37	Very poor	1.46-1.59	56-65
>38	Very, very poor	>1.60	>66

Table 2: Coded value for independent variables

Level	Concentration of MCC pH 102 X1	Concentration of maize starch X2
-1	20%	5%
0	25%	10%
1	30%	15%

Table 3: 3^2 Factorial design layout

Batch code	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Quantitative composition of all formulations from F1 to F9 is presented in *Table 4*. Each formulation was prepared and stored in well closed container for further testing and evaluating optimized formulation.

Physicochemical parameters of co-processed granules obtained from each formulation were determined and these parameters were included appearance, moisture content, Bulk Density, Tapped Density is described in *Table 5*. Carr's index/Hausner ratio, angle of repose and granules friability is presented in *Table 6*, most critical parameter is particle size distribution, and its data for each formulation is given in *Table 7*.

After studying physicochemical parameters of all formulation, granules of each formulation was mixed with lubricant sodium stearyl fumarate at concentration 1% and compressed to obtained placebo tablets. Each set of placebo tablets were again evaluated on physical parameters like weight variation, hardness, friability, wetting time and water absorption ratio, *In-vitro* dispersion time and disintegration time. Data of all above parameter is given in *Tables 8 and 9*.

After evaluating initial physicochemical parameters of granules of all possible formulation (obtained through design expert) and later tablets of placebo granules were prepared to evaluate physical parameters in compressed tablets, formulation F4 was observed optimized one because of excellent micromeritic properties and more than satisfactory results in compressed tablet.

Optimized formulation was selected to combine with active pharmaceutical ingredients to check the effect of API on physicochemical parameters of co-processed granules. Montelukast Sodium was selected as low dose API and Paracetamol as high dose drug substance. Tablets were prepared with both APIs separately.

Both APIs were blended with co-processed granules separately along sweetening agent, coloring, flavoring agents and lubricant followed by compression. Drug content and other physical parameters were determined and data is presented in *Tables 10 and 11*.

Drug content of Montelukast and Paracetamol in Orally Dissolve Tablet were determined by HPLC in *Table 12*.

The administration of oral medications is the preferred route for different drug administration. Recent technological advancements have led scientists to establish Orally Dissolving Tablets (ODTs) with increased adherence and comfort for patients.

Table 4: Formulation (percentage w/w)

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
MCC PH 102	20	20	20	25	25	25	30	30	30
Maize starch	5	10	15	5	10	15	5	10	15
Mannitol	75	70	65	70	65	60	65	60	55
Weight/100 gm	100	100	100	100	100	100	100	100	100
All quantities are expressed in gm									

Table 5: Formulations (Batch size 250 gm)

Sr. No.	Test	F1	F2	F3	F4	F5	F6	F7	F8	F9
		Qty/250 gm								
1	MCC PH 102	50	50	50	62.5	62.5	62.5	75	75	75
2	Maize starch	12.5	25	37.5	12.5	25	37.5	12.5	25	37.5
3	Mannitol	187.5	175	162.5	175	162.5	150	162.5	150	137.5
4	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
All quantities are expressed in gm										

Table 6: Moisture content, Bulk Density(BD) and Tapped Density(TD)

Formulation code	Appearance	Moisture content (%)	Bulk Density(BD)	Tapped Density(TD)
F1	Free flowing granular powder	1.193	0.426 ± 0.32	0.463 ± 0.56
F2		1.096	0.402 ± 0.41	0.441 ± 0.87
F3		1.1	0.399 ± 0.16	0.438 ± 0.53
F4		1.15	0.383 ± 0.19	0.407 ± 0.89
F5		1.471	0.386 ± 0.30	0.424 ± 0.91
F6		1.597	0.430 ± 0.65	0.462 ± 0.17
F7		1.538	0.436 ± 0.96	0.468 ± 0.54
F8		1.562	0.442 ± 0.79	0.475 ± 0.23
F9		1.562	0.440 ± 0.43	0.468 ± 0.39
Mean of three determinations				

Table 7: Hausner ratio, Carr's index, angle of repose and granules friability

Formulation code	Hausner ratio	Carr's index (%age)	Angle of repose	Granules friability (%age)
F1	1.086	8	30 ± 0.72	66 ± 0.32
F2	1.097	9	29 ± 0.42	42 ± 0.66
F3	1.097	9	31 ± 0.63	44 ± 0.67
F4	1.062	6	28 ± 0.58	50 ± 0.54
F5	1.098	9	30 ± 0.72	70 ± 0.34
F6	1.074	7	29 ± 0.69	60 ± 0.87
F7	1.073	7	30 ± 0.12	62 ± 0.24
F8	1.074	7	28 ± 0.22	60 ± 0.91
F9	1.063	6	29 ± 0.19	46 ± 0.37
Mean of three findings				

Table 8: Particle size distribution

Formulation code	Qty retained at 40 mesh	Qty retained at 60 mesh	Qty retained at 80 mesh	Qty retained at 100 mesh	Qty passed through 100 mesh
F1	0.50%	20%	30%	20%	29.50%
F2	0.70%	15%	35%	19%	30.30%
F3	0.20%	18%	32%	18%	31.70%
F4	0.10%	10%	35%	28%	26.90%
F5	0.30%	17%	33%	15%	34.70%

F6	0.30%	18%	30%	14%	37.70%
F7	0.40%	12%	28%	22%	37.60%
F8	0.10%	13%	30%	17%	39.90%
F9	0.20%	14%	34%	13%	38.30%
Mean of three findings					

Table 9: Physicochemical properties of placebo tablet formulations F1 to F9 weight variation, hardness and friability

Formulation code	Weight variation (mg)	Hardness (kp)	Friability
F1	198 ± 0.23	3.8 ± 0.12	0.32%
F2	201 ± 0.45	3.2 ± 0.19	0.45%
F3	204 ± 0.67	3.1 ± 0.21	0.36%
F4	199 ± 0.16	3.5 ± 0.10	0.25%
F5	197 ± 0.92	3.6 ± 0.32	0.54%
F6	201 ± 0.17	3.3 ± 0.41	0.44%
F7	203 ± 0.25	3.2 ± 0.18	0.67%
F8	198 ± 0.54	3.9 ± 0.25	0.53%
F9	202 ± 0.98	3.3 ± 0.38	0.72%
Mean of three findings			

Table 10: Physicochemical properties of placebo tablet formulations F1 to F9 wetting time, absorption ratio *in-vitro* dispersion time and disintegration time

Formulation code	Wetting time (sec)	Absorption ratio	*In-vitro* dispersion time (sec)	Disintegration time (sec)
F1	29 ± 0.34	1.2	87 ± 0.49	54 ± 0.34
F2	32 ± 0.21	0.9	92 ± 0.54	63 ± 0.78
F3	35 ± 0.21	1.3	98 ± 0.65	72 ± 0.35
F4	20 ± 0.21	1.8	60 ± 0.21	40 ± 0.21
F5	32 ± 0.54	0.85	75 ± 0.43	59 ± 0.56
F6	30 ± 0.21	1.18	82 ± 0.62	61 ± 0.43
F7	37 ± 0.21	1.3	88 ± 0.35	69 ± 0.78
F8	29 ± 0.43	0.93	74 ± 0.18	55 ± 0.91
F9	33 ± 0.21	1.29	87 ± 0.29	67 ± 0.39
Mean of three determinations				

Table 11: Montelukast 5 mg Orally Dissolving Tablet (ODT) parameters and results

Parameters	Results
Drug content	100.66%
Weight variation (mg)	201 ± 0.65
Hardness	3.5 kp
Friability	0.38%
Wetting time	25 sec
Absorption ratio	1.5
In-vitro dispersion time	50 sec
Disintegration time	35 sec

Table 12: Paracetamol Orally Dissolving Tablet (ODT) 125 mg

Parameters	Results
Drug content	99.33%
Weight variation (mg)	498 ± 0.42
Hardness	4.5 kp
Friability	0.49%
Wetting time	40 sec
Absorption ratio	1.3
In-vitro dispersion time	60 sec
Disintegration time	40 sec

Orally disintegrating pills is useful for people with swallowing problems (Lindgren S and Janzon L, 1991). Swallowing difficulties are common across all the age groups, and are more specific in pediatric, geriatric, institutionalized, nauseous, and motion sickness illnesses (Sastry SV, *et al.*, 2000). ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

In the present study, co-processed excipients is developed which will be helpful in designing Orally Dissolving Tablet in a very simple way. Co-processed excipient is composed of following main ingredients including mannitol, Microcrystalline Cellulose and maize starch. Some more excipients were added in the final tablet formulation on need basis including flavoring, coloring and sweetening agent. Addition of tablet lubricant is also depending of API properties and it has no effect on any physicochemical parameters of finished tablet.

All above excipient are commonly used in oral disintegrating tablet and but no such combination is available as co-processed excipient although some brand are available like prosolv ODT, pearlitol flash etc.

Formulation was prepared through design expert 32 factorial design. Microcrystalline Cellulose is selected as a binder and maize starch as a disintegrant, both are independent variables, and mannitol is used as diluent. Nine formulations were obtained after applying 32 factorial design and matrix of formulation, level of each factor and quantitative composition is presented in *Tables 1-3.*

Excipients selected for the preparation of co processing by simple conventional wet granulation are generally regarded as safe and are being used in the preparation of orally disintegrating tablets.

Mannitol is widely used in the preparation of Orally Dissolving Tablets because of its various properties that suits Orally Dissolving Tablets like, good mouth feel, soluble in water, non-hygroscopic, inert towards active and other excipients, have low toxicological profile, and its metabolism in the body does not increase the blood glucose level therefor can be used in the diabetic population. As number of the active ingredients have very bitter taste so can cause patient compliance problems in oral drug administration. Mannitol is incorporated in the Orally Dissolving Tablets to avoid taste problems and its water solubility facilitates the rapid Disintegration Time, the most important parameter required for the successful formulation of Orally Dissolving Tablets (Zaid MM, 2018). European Pharmacopoeia defines Orally Dissolving Tablets; as the tablet that must disintegrate in not more than 45 sec.

In the present study mannitol, fine powder is used as a diluent in the preparation of co processed excipient by wet granulation method along with the microcrystalline cellulose PH102 as binder and maize starch as a disintegrant. The combination of filler, binder and disintegrant, is selected and co processed by simple conventional method of wet granulation, to improve the tableting properties specially for Orally Dissolving Tablet dosage form which is the most emerging dosage form in the last two decades, because of its rapid onset of action, no need for water and in the conditions where the patient is unable to ingest the tablet. Mannitol is the choice of excipient in the formulation of Orally Dissolving Tablets because of its negative heat of solution it provides cooling sensation in the mouth, which increase patient compliance.

Another excipient selected for co processing is Microcrystalline Cellulose PH 102 a versatile excipient with dynamic properties in tablet dosage form formulation. In the present study, MCC is used as a binder in the formulation of co processed excipients for Orally Dissolving Tablets. From the literature it is proved that Microcrystalline Cellulose has different functions like binder and disintegrant. Microcrystalline Cellulose provides excellent mouth feel when used in Orally Dissolving Tablets (Saigal N, *et al.*, 2009).

From the literature, it is concluded that Microcrystalline Cellulose has strong binding and disintegrating properties. The disintegrating properties are either due to swelling or capillary action.

In the preparation of Orally Dissolving Tablets, Microcrystalline Cellulose has a greater dilution capacity, than other excipients. The binding properties of Microcrystalline Cellulose are attributable to its plastic deformation during compaction, which occurs by hydrogen bonding with neighboring Microcrystalline Cellulose particles (Al-Khattawi A and Mohammed AR, 2013).

Bi examined the effectiveness of the formulation of orally disintegrating tablets with Microcrystalline Cellulose as a binder due to its high stability and a good mouth taste. Their study found that optimization of the binder disintegrant is essential to reduce the Disintegration Time for formulating Orally Dissolving Tablets.

For Orally Dissolving Tablets maize starch is used as a disintegrant in the preparation of co-processed excipients. It has been shown from the literature that cornstarch has high swelling index and is used in the formulation of a tablet dosage. All of the excipients chosen for this analysis have diversified roles in the tablet dosage form that are cheap and readily available.

Co-processing as proved from the literature is the new and emerging criteria to produce excipients with enhanced properties required for the particular dosage form. It is totally a physical phenomenon and lack any chemical change, so do not require extensive regulatory criteria for use in the dosage form. Through co processing by simple weight granulation method all the selected excipients are mixed and wet granulated to prepare a blend ready to use for direct compression after loading with the active pharmaceutical ingredient in both low and high dose.

Co processed excipients prepared by simple conventional method is evaluated for the flow properties. The powder blend of all formulations from F1 to F9 is evaluated for the properties required for efficient tableting, like moisture content, BD and TD and the results are given in the Table 5 the values given in the table is the mean of the determination of three values. The values of moisture content, Bulk Density and Tapped Density are found in the range of 1.096 to 1.597%, 0.383 to 0.442, and 0.407 to 0.475 respectively.

Hausner ratio, Carr's index, Angle of repose and Granular friability are the key parameters required for successful tableting. These parameters were evaluated for the powder blend formulation for F1 to F9 and the results are given in the Table 6. The values given is the mean of the determination of three values and the results found are in the range of 1.062 to 1.097 for Hausner ratio, 6 to 9 for Carr's index, 28 to 31 for Angle of repose and 42 to 70 for Granular friability.

One of the most important parameter is the particle size distribution that is evaluated for the formulation of co-processed excipients for all formulation from F1 to F9 and the results are given in the Table 7. All the above results of the co processed powder blend show good flow ability and compressibility. After the evaluation of powder blend a placebo tablets of all granules formulation from F1 to F9 is prepared to further evaluate the tableting properties and the results are given in the Tables 8 and 9. Weight variation, hardness, friability, wetting time, absorption ratio, *In-vitro* dispersion and Disintegration Time for all the placebo tablets is found and concluded that F4 is the most robust formulation because of its excellent micromeritic properties and properties in placebo compressed tablets.

Formulation F4 is selected for the loading of active pharmaceutical ingredient, Mountelukast in low and paracetamol in high dose and evaluated for the tableting properties plus drug release profile by HPLC method. The results of the formulation are presented in Tables 10 and

11. The above results show that the tablets are successfully formulated for low and high dose of active pharmaceutical ingredient and qualify the criteria for the Orally Dissolving Tablets.

CONCLUSION

In the present study, effort is made to develop Orally Dissolving Tablet with the help of co processing of cheap and easily available excipients used in the tablet formulation. These excipients were selected according to the need of the dosage form and co processed to improve their functionality.

The combination selected is the new combination of filler, binder and disintegrant processed by conventional wet granulation method. The most robust formulation among all is F4 and percentage w/w concentration of ingredients of co-processed excipient is MCC 25 gm, maize starch 5 gm and mannitol 70 gm.

This combination of the co processed granules were than mixed with the active ingredient in both low and high dose and evaluated for physicochemical properties of Orally Dissolving Tablet and successfully full fill the criteria required for Orally Dissolving Tablets (ODTs).

The tablets prepared from this combination were of sufficient strength with rapid disintegration rate with in the mouth that is less than 45 sec as per European Pharmacopoeia. The method used for the development of co-processed excipient is conventional and cost effective and can be easily applied on shop floor. Commercially available co processed excipients are costly but the present developed excipient for ODTs is cost effective and is the new combination of the excipients with the qualified physicochemical properties required for the development of Orally Dissolving Tablets.

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