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Development of directly compressible co-processed excipients for solid dosage forms

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ABSTRACT

The tablets manufactured by direct compression method using co-processed excipient showed relatively better disintegration time and in vitro drug release, with omission of number of laborious steps as compared to tablets manufactured by conventional wet granulation method. Melt granulation technique is a potential alternative for the development of directly compressible adjuvants. Lactose and mannitol blend (1:1, 1:2, 2:1, 1:3, 3:1; 90, 80 or 70 %) along with meltable binders PVP K – 30 and PEG 4000 (1:9, 1:1 or 9:1) were used in the formulation. The effect of addition of co-processed excipient in a formulation containing poorly compressible drug (paracetamol) was also studied. The micromeritic studies and bulk powder properties of the co-processed agglomerates were studied. It was observed that co-processed agglomerates exhibited much better flow properties as compared to individual excipients. The optimized formulation shows that the tensile strength was found to be inversely related with the percentage of acetaminophen. It might be due to the poor compressibility and elastic recovery of acetaminophen. Lower value of disintegration time may be attributed to decreased tensile strength. No capping and lamination of tablet was observed as usually associated with acetaminophen compression.

Key words: co-processing, excipients, lactose, mannitol, adjuvant, direct compression.

INTRODUCTION

Almost 90% of formulations available in the market are solid oral forms, due to their advantages over other dosage forms [1]. The objective of co-processing is to provide a synergy of functionality improvements [2]. Co-processing is the science of particle engineering of individual excipients, combination of two or more conventional excipients into a single multifunctional/advanced substance of high functionality with superior intrinsic performance -

high compatibility, high intrinsic flow, good lubricating efficiency, improved blending properties and good binding properties [3].

The single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately [4]. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability [5, 6].
Direct compression involves the compression of a dry blend of powders that comprises drugs and various excipients. No pre-treatment of the powder blends by wet or dry granulation is required [7, 8].

Many of the recently co-processed excipients launched into the market for their improved disintegration properties contain mannitol and a superdisintegrant; for example, mannitol co-processed compounds have been developed with crospovidone or with sodium croscarmellose. Examples of co-processed excipients include the lactose compound, calcium carbonate compound, microcrystalline cellulose compound and mannitol compound [9].

The simplicity and cost effectiveness of the direct compression process have positioned direct compression as an attractive alternative to traditional granulation technologies [10]. The demand of excipients with improved functionalities, mainly in terms of flow and compression properties, has increased with the advancement of tablet manufacturing process [11].

MATERIALS AND METHODS

Lactose monohydrate I.P. (Central Drug House Pvt. Ltd. Bombay), Acetaminophen I.P., crospovidone, sodium starch glycolate, polyethylene glycol 4000 (Central Drug House Pvt. Ltd. Bombay), polyvinyl pyrolidone (PVP K 30; Loba Chemie Bombay), Talc I.P. (Genuine Chemicals Co. Bombay), and mannitol (Central Drug House Delhi) were used in the study.

Selection of Binder

Lactose and mannitol blend (1:1, 1:2, 2:1, 1:3, 3:1, 90, 80 or 70 %) were mixed with a blend of 10, 20 or 30 % meltable binder (PVP K – 30, PEG 4000; 1:9, 1:1 or 9:1) in a previously heated porcelain dish on a hot plate maintained at 90 °C. The mixture was heated for 10 min at 90 °C with continuous blending to break the mass into agglomerates, and then the agglomerates were cooled to the room temperature (25 °C). The agglomerates of mesh 30 were collected by sieving and kept in a tightly closed glass jar for until further use. The heating temperature (90 °C), lactose: mannitol ratio (1:1, 1:2, 2:1, 1:3, 3:1, 90, 80 or 70 %) and heating time (10 min) were kept constant in all the formulations. Different ratio and percentage of binder and diluents used for selection of binder is shown in table 1.

Drug Excipients compatibility study

Drug Excipients compatibility study was done by using FTIR spectroscopy and the physical mixture was also observed. A milligram of finely grounded sample was mixed with about 100 mg of dried potassium bromide powder. The IR spectra was taken by KBr disc method using Shimadzu, model 8400-S, Japan.

Table 1 Different ratio and percentage of binder and diluents used for selection of a binder

Binder		Diluent	
Ratio	**Percentage**	**Ratio**	**Percentage**
9:1	10	1:1, 1:3, 2:1	90
	20	1:2, 2:1, 3:1	80
	30	1:1, 2:1, 3:1	70
1:1	10	1:1, 1:3, 2:1	90
	20	1:2, 2:1, 3:1	80
	30	1:1, 2:1, 3:1	70
1:9	10	1:1, 1:3, 2:1	90
	20	1:2, 2:1, 3:1	80
	30	1:1, 2:1, 3:1	70

Agglomeration

The agglomerates were in a laboratory scale 'one step' high shear mixer using meltable binder. Conventional tablets of paracetamol were prepared by using melt granulation method. Hence PEG 4000 and PVK K 30 were used as meltable binder. Composition of different formulations of agglomerates with selected binder with and without drug is given in table 2 and table 3. Accurately weighed quantity of pure drug was mixed with a required quantity of α – lactose monohydrate and a calculated amount of mannitol in a high shear mixer.

Table 2 Composition of different formulations of agglomerates with selected binder without drug

formulations	PEG 4000 (mg)	PVK-30 (mg)	Lactose (mg)	Mannitol (mg)
A	20	20	180.0	180.0
B	20	20	90.0	270.0
C	20	20	240.0	120.0
D	40	40	106.66	213.33
E	40	40	213.33	106.66
F	40	40	240.0	80.0
G	60	60	140.0	140.0
H	60	60	70.0	210.0
I	60	60	186.66	93.33

Table 3 Composition of different formulations of agglomerates with selected binder with drug

formulations	PEG 4000 (mg)	PVK-30 (mg)	Paracetamol (mg)	Lactose (mg)	Mannitol (mg)
AD	20	20	250	180.0	180.0
BD	20	20	250	90.0	270.0
CD	20	20	250	240.0	120.0
DD	40	40	250	106.66	213.33
ED	40	40	250	213.33	106.66
FD	40	40	250	240.0	80.0
GD	60	60	250	140.0	140.0
HD	60	60	250	70.0	210.0
ID	60	60	250	186.66	93.33

Melt granulation in a high shear mixer was a single step technique that converts fine powder into agglomerates combining several processing steps into a single operation unit. The mass was

passed through 10 mesh sieve. The agglomerates were passed through 30 mesh sieve. The even agglomerates were procured.

Characterization of Prepared Agglomerates

The prepared agglomerates were evaluated for different parameters such as Percentage yield, Drug content, Loose Bulk Density, Tapped Bulk Density, Hausner's Ratio, Void volume, Percent Porosity, and Percent Compressibility.

Particle size analysis was done by using optical microscopy and sieving method. The surface area characterization of the solid particles was done by Kozeny – Carmen equation
The sphericity of the powder was calculated from the equation given below

$$\varphi = 3.1129 \times \exp^{(-3.029 \times \text{bed porosity})}$$

Where φ is Sphericity of the powder and 3.1129 is instrument constant

Particle size distribution was performed on random samples of batch FD using a nest of standard sieves (30, 44, 60, 85, 100, 120 mesh). The 30, 44, 60, 85, 100, 120 mesh has 590, 330, 250, 177, 149, 125 µm opening, respectively. The sieves were agitated on an Electromagnetic sieve shaker, EMS-8 for 2 min. From the percentage weight of agglomerates retained on the each sieve, the mean agglomerate diameter was calculated [12].

Loose bulk density was determined by the USP method I; tapped density was determined by USP method II using a tapped density tester (Electrolab, ETD 1020, Mumbai, India) [13]. Hausner's Ratio, Percent Compressibility, Void volume and Percent Porosity were calculated using following Equations:

Hausner's ratio = Dt / Db

Percent Compressibility = Dt – Db / Dt × 100

Where Dt and Db are Tapped bulk density and Loose bulk density

Void volume (v) = Vb – Vp

% porosity (€) = (1 – Vp / Vb) X 100

Where Vb and Vp are Bulk volume (volume before tapping) and Tapped volume (volume after tapping).

The angle of repose was calculated as tan θ = h/r, where θ is angle of repose, h is the height of heap and r is radius of heap.

The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

The loss in drying was calculated as percent loss = $\Delta W / W_1 \times 100$

Where ΔW is difference between before and after drying and W_1 is the weight before drying.

Formulation of Tablets

Tablets were compressed by using 8 mm diameter flat faced punches and die on a single punch tablet compression machine (Cadmach Machinery Pvt. Ltd., Ahmedabad). The average weight of the placebo and non placebo tablets was 400 mg and 650 mg respectively. The minimum distance between upper and lower punch was between 0.26 and 0.28 cm during preparation of tablets.

Evaluation of Tablets

Uniformity of weight

USP procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance (Shimadzu, AW 220). The average weight of one tablet was determined from the collective weight [14].

Tablet Hardness

The hardness of each tablet formulation was determined by using Digital Force Gauge, Electrolab, EL – 500. [15]

Friability Test

Friability of the prepared tablets was evaluated as the percentage weight loss of twenty tablets tumbled in a friabilator (model EF2, Electrolab, India) for 4 min at 25 rpm. [15]

$$\text{Friability } (\%) = \frac{(\text{Initial weight of 20 tablets} - \text{Final weight of 20 tablets})}{\text{Initial weight of 20 tablets}} \times 100$$

Tensile Strength

The dimensions of the prepared tablets were measured by using a digimatic micrometer, (Mitutoyo, Japan). The crushing strength was determined after 24 h of compression, by using a monsanto hardness tester (Shital Scientific Industries, Bombay, India). [12]

$$F = \frac{(0.0624 \times P)}{D \times L}$$

Where, D is diameter of the tablet (cm), L is length of the tablet (cm), P is Crushing strength of the tablet (kg) and F is Tensil strength (MPa).

Disintegration Test

Disintegration test (Model ED 2; Electrolab India) for the prepared tablets was performed at 37 °C in 900 mL of phosphate buffer pH 5.8 for six tablets in accordance with the USP 2007 [14].

Assay of prepared paracetamol tablets

The content of parecetamol present in the prepared tablets was determined by Single Beam UV Visible Spectrophotometer (Shimadzu, Model 119, Japan). The absorbance of the diluted solution was measured at 257 nm [16].

Amount of drug present in a tablet = Concentration × Dilution Factor × Average weight of the tablet × Potency.

***In vitro* dissolution Studies**

In vitro dissolution study for fabricated FDTs was carried out by using USP Dissolution Apparatus II paddle type at 50 rpm in 500 ml of SGF as dissolution media, maintained at 37±0.5 ^{0}C. The study was carried for 1 h and at predetermined time intervals (0, 5, 10, 15, 30, 45, 60, minutes) 5 ml aliquots were withdrawn, filtered and assayed spectrophotometrically at λ max 234 nm using double beam UV Visible Spectrophotometer (Shimadzu, Model 1700, Japan). An equal volume of fresh medium, which was pre-warmed at 37 °C, was replaced into the dissolution medium after each sampling to maintain the sink condition throughout the study. Dissolution study was performed in triplicate for each formulation.

Dilution Potential

Dilution potential is the amount of poorly compressible drug that can be satisfactorily compressed into the tablet with a directly compressible adjuvant. Dilution potential of agglomerates of formulation FD was evaluated by using paracetamol as model drug [12].

Table 4 Dilution Potential study of various batches of optimized formulation

Ingredients	Formulations			
	FD 1	FD 2	FD 3	FS 4
Agglomerates of formulation FD (%)	90	80	70	60
Paracetamol (%)	5	15	25	35
Crospovidone (%)	2	2	2	2
Talc (%)	2	2	2	2
Magnesium Stearate (%)	1	1	1	1

A comparison study was done in between the formulations prepared by direct compression and wet granulation method. Wet granulation technique was used to develop the agglomerates of final optimized batch of agglomerates and tablets were evaluated.

Stability Studies

The prepared paracetamol tablets of optimized batch (FD) were packed in suitable packing and stored at temperature (40 °C ± 1 °C) and relative humidity (75 % ± 5 %) for a period of 45 days for accelerated stability study in environmental test chamber (Macro Scientific Works, New Delhi). The tablets were withdrawn after a period of 45 days and analyzed for physical characterization, (visual defect, tensile strength, hardness, friability, disintegration, dissolution) and drug content.

RESULTS AND DISCUSSION

The physical mixture was observed for physical changes (discoloration and caking). The physical mixture showed no sign of discoloration and caking after two weeks and percentage recovery of drug was found to be 100.4 %. No significant changes were found when IR spectra of physical mixture compared with IR spectrum of pure drug and excipient. This indicates absence of any possible interaction between the drug and excipient system.

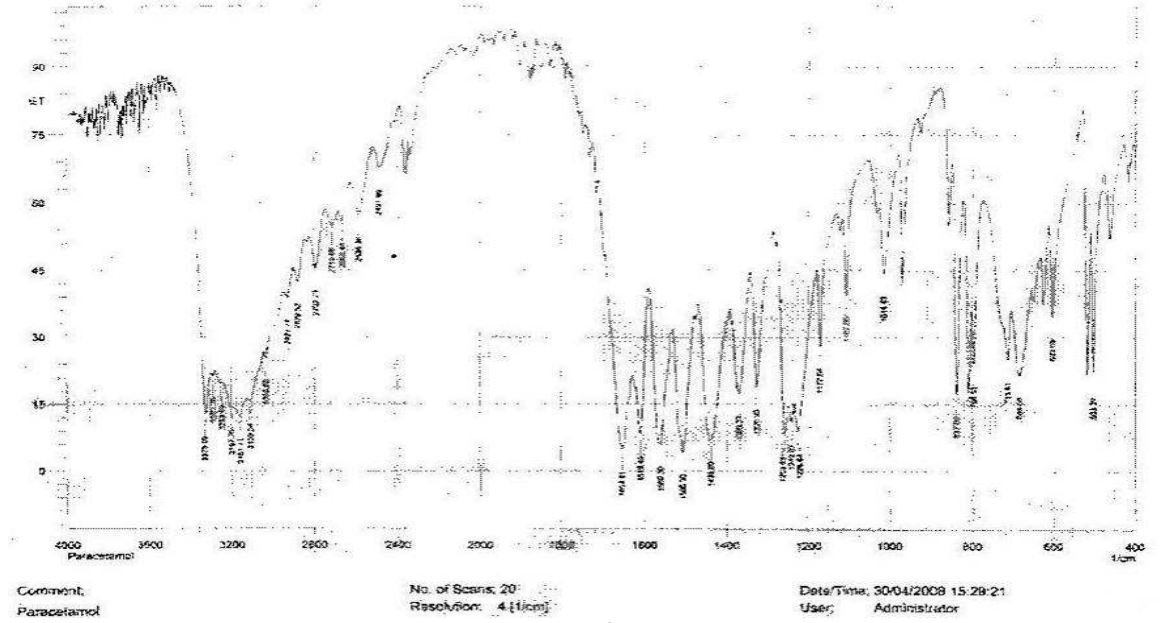

Figure 1 IR spectra of pure paracetamol

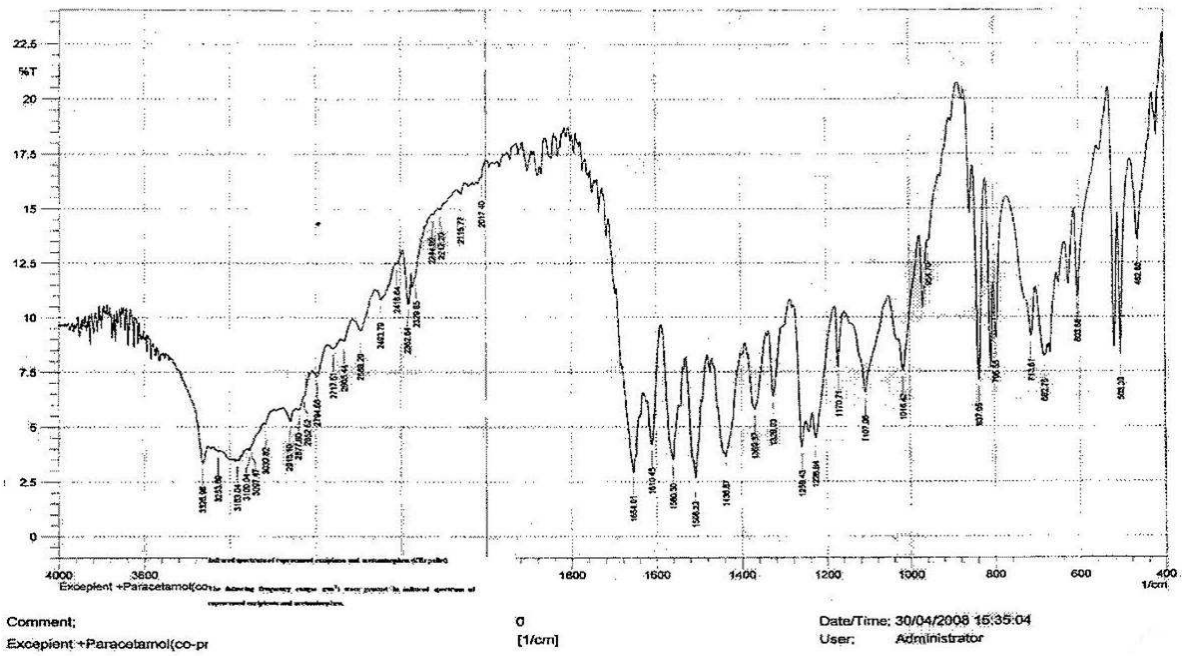

Figure 2 IR spectra of co-processed excipients and paracetamol

The effect of different ratio and percentage of binders and diluents in the formulation of agglomerates is summarized in table 5. It is clear that only 1:1 of the binder was suitable for the formation of agglomerates. Hence this ratio of binder 1:1 (10, 20 and 30 %) had been selected for formation of different formulations with different ratio of diluents 1:1, 1:3, 2:1 (90, 80 and 70 %), 1:2, 2: 1, 3:1 (90, 80 and 70 %), 1:1, 1:3, 2:1 (90, 80 and 70 %) respectively.

Table 5 The effect of different ratio and percentage of binders and diluents in the formulation of Agglomerates

Binder		Diluent		Observations
Ratio	Percentage	Ratio	Percentage	
9:1	10	1:1, 1:3, 2:1	90	Excess percentage of fines was present. No agglomerates were formed.
	20	1:2, 2:1, 3:1	80	
	30	1:1, 2:1, 3:1	70	
1:1	10	1:1, 1:3, 2:1	90	Agglomerates were formed.
	20	1:2, 2:1, 3:1	80	
	30	1:1, 2:1, 3:1	70	
1:9	10	1:1, 1:3, 2:1	90	Molten mass formed which upon cooling were not form agglomerates
	20	1:2, 2:1, 3:1	80	
	30	1:1, 2:1, 3:1	70	

Table 6 Particle size analysis of pure polymer (PEG 4000)

Size group of counted particle (µm)	Middle Value (d)	No. of particles per group (n)	nd
0 – 10	5	30	150
10 – 20	15	150	2250
20 – 30	25	130	3250
30 – 40	35	60	2100
40 – 50	45	50	2250
50 – 60	55	20	1100
60 - 70	65	20	1300
		Σn = 460	Σnd = 12400

Table 7 Particle size analysis of pure polymer PVP K 30

Size group of counted particle (µm)	Middle Value (d)	No. of particles per group (n)	nd
0 – 2	1	5	5
2 – 4	3	35	105
4 – 6	5	100	500
6 – 8	7	80	560
8 – 10	9	45	405
10 – 12	11	10	110
12 – 14	13	5	65
		Σn = 280	Σnd 1750

Particle Size Analysis

The average particle size of pure polymer (PEG 4000) and pure polymer (PVP K-30) was found to be 26.95 µm (Table 6) and 6.25 µm (Table 7) respectively. The average particle size of pure

drug (paracetamol) was found to be 6.00 µm (Table 8) and the particle size of the agglomerates of the optimized formulation was found to be 170.45 µm (Table 9).

Table 8 Particle size analysis of pure drug

Size group of counted particle (µm)	Middle Value (d)	No. of particles per group (n)	nd
0 – 2	1	30	30
2 – 4	3	80	240
4 – 6	5	130	650
6 – 8	7	90	630
8 – 10	9	40	360
10 – 12	11	30	330
12 – 14	13	10	130
14 - 16	15	10	150
		Σn = 420	Σnd = 2520

Table 9 Particle size analysis of agglomerates of optimized formulation

Size group of counted particle (µm)	Middle Value (d)	No. of particles per group (n)	nd
0 – 50	25	20	500
50 – 100	75	40	3000
100 – 150	125	60	7500
150 – 200	175	100	17500
200 – 250	225	70	15750
250 – 300	275	20	5500
300 - 350	325	20	6500
		Σn = 330	Σnd = 56250

Table 10 Particle size distribution of co-processed excipients

Formulation	Percentage agglomerates retained on mesh					
	30	**44**	**60**	**85**	**100**	**120**
A	0.1	2.2	25.2	42.1	20.2	8.0
B	0.2	1.2	19.1	45.0	26.9	6.0
C	0.3	2.6	23.8	36.3	25.6	9.9
D	0.5	1.7	27.9	39.7	24.8	4.0
E	0.8	2.7	20.3	39.9	30.3	4.0
F	0.2	2.1	35.0	37.1	22.9	1.0
G	0.2	3.0	31.2	44.6	18.7	1.0
H	0.6	2.3	28.6	39.1	25.1	5.0
I	1.0	5.9	33.9	34.6	21.0	2.0

It was decided to select the formulation that show percentage fines < 20 %. The formulation containing a low level of meltable binder showed a higher percentage of fines. It was worthwhile to note that inverse relationship was observed between the amount of binder and percentage fines. From the results it may be concluded that both the ratio and percentage of binder should be critically controlled to obtain agglomerates of sufficient strength (Table 10 and Table 11).

Powder characterization

The percentage compressibility (Carr's index) between 5 to 15 and 15 to 20 indicates excellent good and good flow ability respectively. Although value > 30 % indicates poor flow,

agglomerates of all the formulations AD, BD and CD exhibited Carr's index < 30 %; good flow. The unsatisfactory flow of formulations AD, BD and CD may be due to the presence of excess of small particles (Table 12 and Table 13).

Table 11 Particle size distribution of co-processed excipients with drug

Formulation	Percentage agglomerates retained on mesh					
	30	**44**	**60**	**85**	**100**	**120**
AD	0.1	4.2	28.2	31.1	23.2	12.0
BD	0.1	3.2	21.9	33.2	30.2	10.0
CD	0.1	3.8	22.2	25.1	32.4	15.0
DD	0.1	2.8	29.2	35.1	23.1	8.0
ED	0.2	5.6	20.1	30.3	36.1	6.0
FD	0.1	3.5	17.9	28.2	45.6	3.0
GD	2.1	7.1	31.2	32.0	24.1	2.0
HD	1.0	4.3	24.2	40.0	21.5	6.0
ID	2.1	8.3	31.1	27.2	26.0	4.0

Table 12 Powder characterization of various co-processed excipients

Micromeritic properties	Formulations								
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Bulk Density (ρ) (g/cm^3)	0.39	0.49	0.41	0.51	0.58	0.53	0.43	0.52	0.51
Tapped Density (ρ) (g/cm^3)	0.64	0.71	0.60	0.64	0.77	0.60	0.52	0.63	0.58
Solid Density (ρ) (g/cm^3)	1.25	1.26	1.15	1.32	1.19	1.09	1.26	1.35	1.15
Compressibility (%)	39.06	30.98	31.66	20.31	24.67	11.66	17.30	17.43	12.06
Sphericity (φ)	0.64	0.69	0.59	0.62	0.68	0.76	0.51	0.57	0.66
Bed porosity (ε)	0.52	0.49	0.55	0.53	0.50	0.47	0.51	0.55	0.51
Angle of repose (θ)	30.01	30.04	31.01	23.07	23.95	15.02	17.01	20.50	19.09
Flowability *	++	+	+	+	+	++	+	+	++
Fines (%)	8	6	9.9	4	4	1	1	5	2
Solid surface area (cm^2/g)	7528	7264	9785	7989.3	7720	1188	10489	8528	7879
Housner Ratio (HR)	1.64	1.44	1.46	1.25	1.32	1.13	1.20	1.21	1.13

** ++ indicates excellent flow, + indicates fairly free flow*

Loss on Drying (%)

The result indicates that there was no significant absorption of moisture from the atmosphere (table 14).

Table 14 Loss on drying (%) of different ingredients and optimized formulation

Ingredients	Loss on drying (%)
PVP K 30	0.10
Paracetamol	0.50
Agglomerates of optimized formulation	0.40

Table 13 Powder characterization of various co-processed excipients with drug

Micromeritic properties	Formulations								
	AD	**BD**	**CD**	**DD**	**ED**	**FD**	**GD**	**HD**	**ID**
Bulk Density (ρ) (g/cm^3)	0.49	0.50	0.46	0.58	0.62	0.60	0.49	0.65	0.57
Tapped Density (ρ) (g/cm^3)	0.84	0.89	0.81	0.80	0.85	0.75	0.63	0.88	0.74
Solid Density (ρ) (g/cm^3)	1.21	1.24	1.23	1.15	1.17	1.25	1.32	1.20	1.09
Compressibility (%)	41.66	43.82	43.21	27.50	27.05	20.00	22.22	26.13	22.97
Sphericity (φ)	0.31	0.59	0.61	0.55	0.50	0.50	0.60	0.53	0.43
Bed porosity (ε)	0.76	0.54	0.54	0.57	0.60	0.57	0.54	0.58	0.65
Angle of repose (θ)	31.01	30.05	33.02	25.03	26.03	16.11	18.12	22.00	21.01
Flowability *	-	±	-	+	+	+	+	+	+
Fines (%)	12	10	15	8	6	3	2	6	4
Solid surface area (cm^2/g)	26241	8744	8095.5	10672	10124	1261	8192	1205	3047
Housner Ratio (HR)	1.71	1.78	1.76	1.38	1.37	1.25	1.28	1.35	1.29

** ± indicates excellent flow, + indicates fairly free flow*

Evaluation of tablets

The tablets of formulations AD to ID exhibited friability < 0.90 %. It can be due to the binder had negative effect on friability. The tablets of formulations GD, HD and ID exhibited relatively high values of disintegration time (> 20 min). This might be due to higher tensile strength of the tablet and higher percentage of polyethylene glycol.

From the above findings, it can be concluded that both the percentage binder and ratio of diluents are important for the preparation of directly compressible adjuvant with high yield (low fines), good flowability (low Carr's index) and satisfactory tablet characteristics (Table 15 and Table 16). The prepared tablets were assayed and results of the study are shown in table 17.

Table 15 Evaluation on tablets of co-processed excipients mixture without drug

Formulation	Average weight of tablet (mg)	Hardness (kg)	Tensile strength (MPa)	Friability (%)	Disintegration time (min)
A	402	3.5	0.865	0.53	3.5
B	402	3.5	0.889	0.74	5.0
C	405	4.0	1.004	0.62	4.0
D	398	4.0	1.004	0.51	6.5
E	398	5.0	1.050	0.67	7.0
F	402	4.0	1.046	0.42	5.5
G	404	6.0	1.460	0.73	12.0
H	401	6.5	1.298	0.57	25.0
I	405	6.0	1.460	0.64	30.0

Table 16 Evaluation on tablets of co-processed excipients mixture without drug

Formulation	Average weight of tablet (mg)	Hardness (kg)	Tensile strength (MPa)	Friability (%)	Disintegration time (min)
AD	652	4.0	1.165	0.63	8.5
BD	652	4.5	1.059	0.64	10.0
CD	650	5.0	1.120	0.72	9.0
DD	648	4.0	1.124	0.68	9.5
ED	648	5.0	1.250	0.67	9.0
FD	650	4.0	1.050	0.50	7.0
GD	652	5.0	1.560	0.83	15.0
HD	651	6.0	1.498	0.87	30.0
ID	650	6.5	1.260	0.90	35.0

Table 17 Assay of paracetamol tablets of various formulations

Formulations	Amount of drug present in a tablet (mg)
AD	245.10
BD	246.81
CD	249.03
DD	245.40
ED	245.02
FD	246.81
GD	248.41
HD	247.20
ID	249.30

In vitro dissolution Study

From the data of evaluation of tablets (placebo and non placebo) as shown in table 18, it is clear that among all the tablets (placebo and non placebo), batch FD exhibited minimum disintegration time and maximum *in vitro* drug release in phosphate buffer of pH 5.8 with optimum hardness, friability and tensile strength. It may be due to presence of hydrophilic binder (20 %) and co-processed diluents (mannitol and lactose) in ratio 3:1.

Table 18 Cumulative percentage release of drug from different formulations in phosphate buffer pH 5.8

Time interval (min)	Formulations (Mean ± S.D.)								
	AD	**BD**	**CD**	**DD**	**ED**	**FD**	**GD**	**HD**	**ID**
5	7.36 ± 0.48	16.31 ±7.82	13.51 ±0.88	15.86 ±3.34	18.52 ±8.49	14.30 ±5.06	16.15 ±4.79	4.67 ±1.52	15.07 ±1.42
10	22.90 ±5.75	28.54 ±6.08	28.99 ±1.4	27.41 ±4.34	37.13 ±3.17	29.95 ±3.88	26.09 ±3.24	9.59 ±4.74	19.07 ±1.29
15	50.87 ±5.47	43.37 ±6.04	35.58 ±2.7	41.25 ±9.53	44.78 ±0.04	65.73 ±2.31	28.90 ±4.06	21.19 ±6.99	29.99 ±5.64
20	64.98 ±5.46	62.28 ±9.5	61.57 ±2.8	54.16 ±5.48	53.16 ±9.89	76.01 ±1.13	36.68 ±9.64	32.19 ±7.13	37.58 ±7.6
25	74.96 ±3.44	73.43 ±0.94	66.09 ±4.2	72.49 ±7.33	69.39 ±3.82	82.76 ±3.80	39.19 ±3.28	52.8 ±7.83	44.04 ±6.41
30	78.99 ±5.45	76.95 ±3.35	79.99 ±6.7	88.45 ±7.02	82.92 ±5.34	92.04 ±4.37	49.68 ±1.97	60.14 ±9.89	65.21 ±5.58

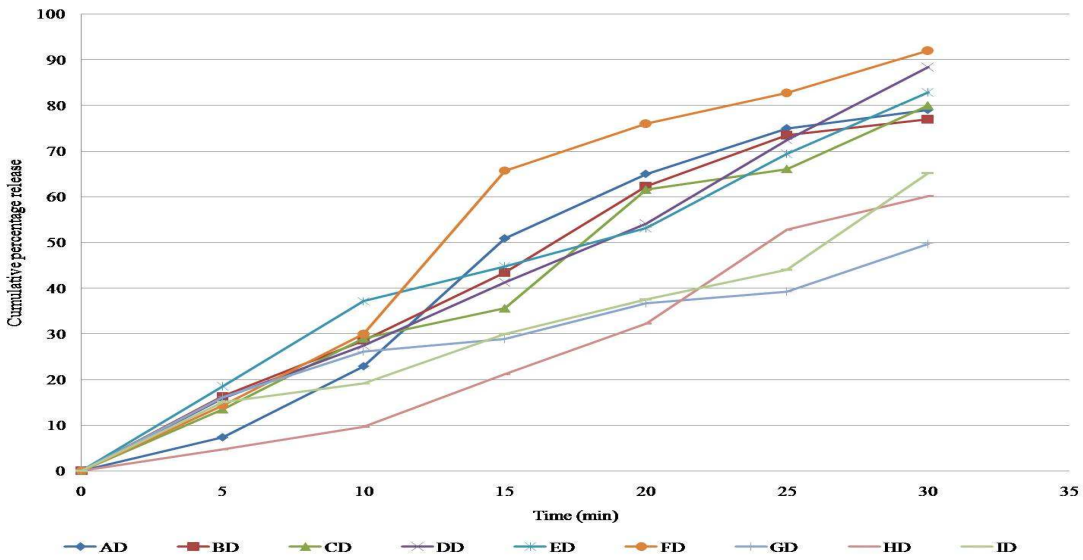

Figure 3 Cumulative percentage release of drug from different formulations in phosphate buffer pH 5.8

Dilution Potential

Tablets were prepared by using 5-35 % paracetamol. It was arbitrarily decided to select a batch, which shows friability < 1 %. It was quite evident from the result shows that 35 % paracetamol gave acceptable results (Table 19).

Table 19 Evaluation of tablets of various optimized formulation

Formulations	Hardness (kg)	Friability (%)	Disintegration time (min)	Tensile strength (MPa)
FD 1	4.00	0.43	6.00	1.00
FD 2	3.80	0.52	5.00	0.90
FD 3	3.50	0.63	4.00	0.85
FD 4	3.00	0.83	3.00	0.50

Table 20 Evaluation of optimized formulation FD after a period of 45 days

Sl. No.	Parameters	Observations
1	Physical appearance	White, biconcave
2	Average weight of tablets (mg)	652.00
3	Friability (%)	0.49
4	Hardness (kg)	3.90
5	Tensile strength (MPa)	1.00
6	Drug content (mg)	246.80
7	Disintegration time (min)	7.00

Stability Studies

The results were determined after withdrawal of optimized formulation FD after a period of 45 days, are shown in table 20 and table 21. There was no capping and lamination was observed in any tablet of the optimized formulation. From the stability study of the optimized formulation;

hardness, tensile strength, friability and drug content were found within prescribed limits as per I.P. and there was no difference found in disintegration time and *in vitro* drug release after stability study.

Table 21 *In vitro* dissolution of optimized formulation FD in phosphate buffer pH 5.8 after a period of 45 days

Time (min)	Percentage Release
0	0
5	14.02
10	29.01
15	55.91
20	75.10
25	82.05
30	91.50

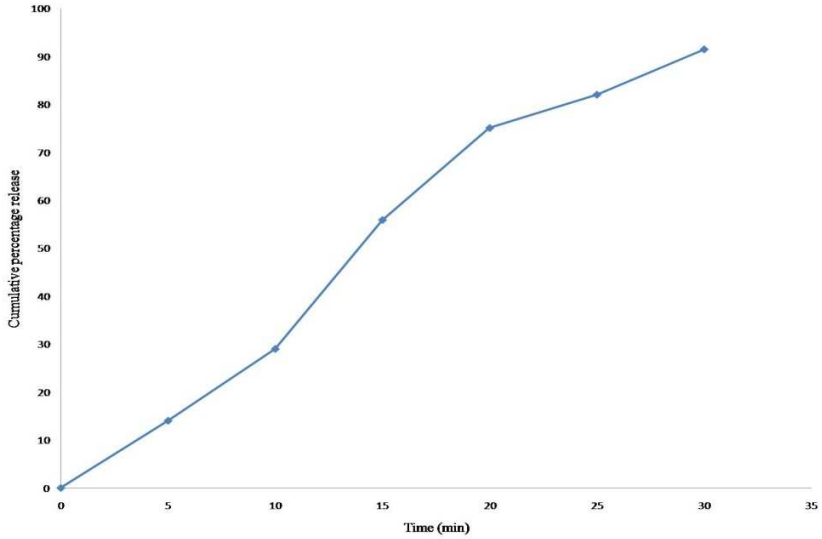

Figure 4 Percentage release of drug from optimized formulation FD in phosphate buffer pH 5.8 after a period of 45 days

CONCLUSION

Co-processed excipients were prepared by incorporating one excipient into the particle structure of other excipient using melt granulation technique. Thus co-processed excipients are simple physical mixture of two or more existing excipients mixed at the particle level. In the present study we found that co-processing of mannitol and lactose with the help of meltable polymer PVP K-30 and PEG 4000 (at 1:1 ratio) produces superior properties. Since mannitol has good aqueous solubility, but high friability. We have combined it with it with lactose which has better compressibility and water absorption properties leading to co-processed excipients with less friability and better flowability due to meltable polymer like PVP K-30 and PEG. The tablets prepared by co-processed excipient exhibited relatively higher disintegration time due to the presence of higher percentage of meltable binder modulation of the disintegration time was done by incorporating crospovidone.

From the dilution potential study of optimized formulation, it was concluded that the tensile strength was found to be related with the percentage of paracetamol. It might be due to poor compressibility and elastic recovery of paracetamol. Tablets containing poorly compressible drug (paracetamol) were manufactured by direct compression method using optimized co-processed combination, showed relatively better disintegration time and *in vitro* drug release. From the study it can be concluded that co-processed excipient can be used as a compressible diluents for poorly compressible drugs.

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