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An Investigation of Direct Compression Characteristics of Co-processed Lactose-Starch Using Factorial Design

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Present investigation was aimed to prepare economical lactose based directly compressible adjuvant with improved flowability and compressibility. A 3^2 full factorial design was employed to study the effect of lactose/starch ratio (X_1; 50:50, 65:35 or 80:20) and the % starch paste (X_2; 6, 10, or 14 %). Starch paste was prepared by heating the aqueous dispersion of starch at 80° for 15 min. The paste was used to prepare granules. Tablets were prepared on a single stroke tablet machine. The % fines, Carr's index, granular friability, crushing strength and % friability were selected as the dependent variables. Diltiazem HCl and acetaminophen were used as model drugs for evaluating the characteristics of the optimized batch. Medium to high level of both the variables favoured the formation of excellent directly compressible adjuvant. The lactose/starch ratio (X_1) exhibited greatest effect on the crushing strength, Carr's index and tablet friability. As the lactose/starch ratio was increased, Carr's index and crushing strength of the tablets increased and friability of the tablets decreased. The friability of the tablets was inversely related with % of starch paste. A check-point batch was prepared to validate evolved refined models. Good agreement was observed between actual and predicated values of the dependent variables, indicating predictive power of the derived equations. Starch paste prepared by the conventional method yielded weak tablets. Kawakita's and Kuno's parameters suggest that the granules of the check-point batch undergo packing at faster rate than the physical blend of lactose and starch. Up to 30% of acetaminophen could be successfully incorporated into tablets. The crushing strength, friability and disintegration time of diltiazem HCl tablets were found 5.5 kg, 0.5% and 4 min, respectively. Nearly complete release of diltiazem HCl was observed in 15 min in water. The preparative conditions of starch paste determine the product quality. The present study demonstrates the use of experimental design for the preparation of an economical directly compressible adjuvant. The results of multiple regression analysis can be used to predict the effect of independent variables on the dependent variables. A product consisting of (lactose/starch ratio-71:29) exhibited excellent functionality and good tableting characteristics. The developed product can be explored as an economical alternative to the other lactose based directly compressible adjuvants available in the market.

Direct compression requires fewer processing steps, offers simplified validation, improved drug stability due to elimination of heat and moisture and economy compared to the wet granulation technology[1]. Introduction of high speed tablet machine and force feeder mechanism increased the interest of pharmaceutical manufacturers in directly compressible adjuvant steadily over the years. Di-

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rectly compressible filler must possess good compressibility and flowability to ensure that the compact formed remain bonded after the compaction pressure is removed and all the compacts in the lot have uniform weight respectively. Today, majority of directly compressible adjuvants are prepared by co-processing. The excipient mixture prepared by co-processing has enhanced functionality over to the simple physical blend of the component excipients[2]. Some of the available co-processed adjuvants are Cellactose[R], Ludipress[R], and StarLac[R].

Commercially available α-lactose monohydrate is not suitable for direct compression because it lacks essential fluidity and compressibility[3]. Lactose is an excipient of choice for direct compression because it is more compressible and less hygroscopic than sugars (i.e. sucrose and sorbitol), and physiologically inert than the calcium containing diluents (i.e. dicalcium phosphate dihydrate or tricalcium phosphate). Starch is used in oral solid dosage form as a binder, diluent and disintegrant[4]. It is physiologically inert, compatible with wide range of drugs, readily available, and probably cheapest in all the excipient used as a filler-binder. Starch also lacks flow and compressibility.

One of the product available in international market is StarLac[R] (Roquette, France) consists of α-lactose monohydrate (85%) and maize starch (15%). It is probably prepared by spray drying. The spray drying is relatively complicated and expensive than classical granulation. One of the objectives of present work was to develop a process that can be adopted by the small-scale pharmaceutical industry. Directly compressible diluents can be prepared by grinding, sieving, crystallization, spray drying, granulation, pregelatinization, dehydration and enzymatic reaction[2]. In the present investigation granulation was adopted.

Present investigation was aimed to prepare a lactose based directly compressible diluent with improved flowability and compressibility than the commercially available lactose but at the comparable price as that of commercially available lactose. In present study lactose and starch were selected to develop the one-body adjuvant having filler-binder and built-in disintegrant characteristics. Hence, the adjuvant eliminates the requirement of an extra disintegrant. Thereby, use of product of present study can reduce the cost of the final formulation. Another objective was to study the effect of variables on the functionality of the directly compressible adjuvant.

MATERIALS AND METHODS

Lactose monohydrate IP of average particle size, 96 μ was obtained from Vikas Pharma, Mumbai. Cornstarch IP was procured from Anil Starch, Ahmedabad. Diltiazem hydrochloride USP was a gift from Cadila Healthcare Private Ltd., Ahmedabad. Magnesium stearate IP from Apex Chemicals, Ahmedabad and talc IP from JC Chemicals, Vadodara were used as received.

Experimental design:

A 3^2 full factorial design was employed to study the effect of lactose/starch ratio (X_1) and the percentage of starch paste (X_2) at three different levels i.e. low (-1), medium (0) and high (+1). The quantity of starch paste (100 ml), quantity of the powder blend (100 g), mixing time (10 min) and drying conditions (60°, 2 h) were kept constant in all the trials. The % fines, % Carr's index, granular friability, crushing strength and % friability selected as the dependent variables. The design layout and results are shown in Table 1 and Table 2, respectively.

Granulation:

Starch (6, 10 or 14 g) was dispersed in 100 ml distilled water at ambient condition and heated on a water bath for at 80° for 15 min to obtain a gel of binder solution. Lactose and starch blend (100 g, lactose/starch ratio 50:50, 65:35 or 80:20) was blended with sufficient amount of the binder solution to obtain a damp mass suitable for granulation. The damp mass was passed through a 44-mesh and the granules were allowed to dry at 60° for 2 h in a hot air oven. The dried granules were resifted through a 44 mesh and retained on 200 mesh. The granules of 44/200 were kept in airtight containers till further use (Batch M1- M10). The amount of granules passed through the 200 mesh was noted as percentage fines. The Carr's index (% compressibility) was calculated as one hundred times the ratio of the difference between tapped density and bulk density to the tapped density[5].

Granular friability:

Twenty-five grams of granules were subjected to friabilator (model EF2, Electrolab, Mumbai) at 25 rpm. After 4 min, the granules were again sieved on a 200 mesh. The amount of granules passed through 200 mesh was calculated as % granular friability[6].

Preparation of tablets:

Tablets were prepared containing granules of batch M1-

TABLE 1: DESIGN LAYOUT AND COMPOSTION OF THE BATCHES M1-M10.

Batch	Variables in Coded level		Actual Values of Variables	
	Lactose/ starch ratio (X_1)	% Starch paste (X_2)	Lactose/ starch ratio (X_1)	% Starch paste (X_2)
M1	-1	-1	50:50	6
M2	-1	0	50:50	10
M3	-1	1	50:50	14
M4	0	-1	65:35	6
M5	0	0	65:35	10
M6	0	1	65:35	14
M7	1	-1	80:20	6
M8	1	0	80:20	10
M9	1	1	80:20	14
M10*	0.4	0.5	71:29	12
Variables		Level		
		Low (-)	Intermediate (0)	High (+1)
Lactose: starch ratio (X_1)		50:50	65:35	80:20
% Starch paste (X_2)		6	10	14

*M10 is the checkpoint batch.

M11 (97 %), talc (2 %) and magnesium stearate (1 %) using 8 mm flat faced punches on a single punch tablet machine. The average weight of the tablets was kept 250 mg. The tablets were evaluated for crushing strength and friability. The results are shown in Table 2.

Crushing strength and friability:

Crushing strength was determined, 24 h after compression (time for stress relaxation) using a crushing strength tester (Shital Scientific Industries, Mumbai)[7]. Twenty tablets were subject to the friabilator at 25 rpm. After 4 min, tablets were dedusted and weighed. The percentage weight loss was noted as percentage friability[8]. From the results of factorial design contour plot was generated. The checkpoint (batch M10) was prepared to validate the evolved model. The composition and result of parameters of batch M10 are shown in Tables 1 and 2, respectively. The granules of batch M10 was evaluated for particle size distribution, granular friability rate constant, Kawakita's and Kuno's parameters and tableting with model drug.

Effect of heating condition:

An additional batch (M11, lactose/starch ratio-71:29) was prepared using 12% w/v starch paste, which was prepared by the conventional method. Briefly, starch (12 g) was dispersed in cold water (20 ml). On the other hand 80 ml of water was heated to 70°. The starch dispersion was added to hot water and heating was continued for another 2-3 min. The translucent mass was used for granulation of blend of lactose/starch (71:29). The remaining procedure was identical to that used for preparation of batch M10.

Particle size distribution:

Particle size distribution was performed on a random sample of batch M10 using nest of standard sieves (44, 60, 85, 100, 120, 200 mesh). The sieves were agitated on a rotap sieve shaker (International Combustion Ltd., London) for 2 min. From the percentage weight retained on each sieve, the mean granule size was calculated[9].

Granular friability rate constant:

The friability index provides the means of measuring the propensity of granules to break into smaller pieces when subjected to disruptive forces. Granules (25 g) of batch M10 were subjected to the friabilator (model EF2, Electrolab, Mumbai) at rotational speed of 25 rpm. After 5, 15, 30, 45,

60, 75 and 90 min the granules were removed from the friabilator and the mean particle size of the granules after each time interval calculated as described above. The friability index was calculated as the ratio of mean particle size of friabilator treated granules to the untreated granules. The negative natural logarithm of friability index was plotted against the time. Slope of this line gave the friability rate constant[10, 11]

Kawakita's and Kuno's parameters:

The packability was evaluated by tapping the agglomerates in a measuring cylinder. The data were analysed using Kawakita and Ludde's[12] and Kuno's[13] equations 1 and 2, respectively. $n/c=1/ab+n/a$, $a=V_0-V_{inf}/V_0$, $c=V_0-V_n/V_0$---(1) and $P_f-P_n=(r_f-r_o)\exp(-kn)$---(2), where P_o, P_n and r_f are the apparent densities at initial state, after nth tapping (5, 10, 15, 20, 25, 50, 75, 100, 200, 300, 400) and equilibrium (500th tap), respectively and k is a constant.

Dilution potential:

Dilution potential is the amount of poorly compressible drug that can be satisfactorily compressed into a tablet with directly compressible adjuvant. Dilution potential of agglomerates of batch M10 was evaluated using acetaminophen as a model poorly compressible drug. The agglomerates of batch M10 (212.5, 187.5 or 162.5 mg) was mixed with acetaminophen (25, 50 or 75 mg, respectively) for 5 min. The blend was mixed with Cab-O-Sil (10 mg), talc (10 mg) for 2 min and then with magnesium stearate (5 mg) for 1 min. The mass was compressed into tablets using 8 mm flat-faced punches. The average weight of tablets was kept 250 mg.

Preparation of diltiazem HCl tablets:

Diltiazem HCl was selected as a model drug to ascertain the tableting characteristics of the granules of batch M10. Granules of batch M10 (185 mg) were mixed with diltiazem HCl (60 mg) for 5 min. The blend was mixed with talc (2.5 mg) and magnesium stearate (2.5 mg) for 1 min. The powder was compressed into tablets using 8 mm flat faced punches on a single punch tablet machine. The average weight of the tablets was 250 mg. Tablets were evaluated for following parameters apart from the crushing strength and friability.

Disintegration test and *in vitro* drug release:

Disintegration test was performed in a disintegrating apparatus (model ED2, Electrolab, Mumbai, India) at 37° in 900 ml distilled water for 6 tablets in accordance with the USP 24[14]. The *in vitro* dissolution study of tablets containing diltiazem HCl was performed using dissolution apparatus (model TDT- 60T, Electrolab, Mumbai) fitted with paddles

TABLE 2: RESULTS OF 3^2 FULL FACTORIAL DESIGN (BATCH M1-M9) AND BATCH M10-M11.

Batch	Fine (%)	Carr's Index (%)	Granular Friability(%)	Crushing Strength (kg)	Friability(%)	Composite Index
M1	6.66	6.98	2.33	0.5	10.45	15.01
M2	4.58	5.8	1.85	2.0	6.92	49.53
M3	3.54	6.25	0.66	2.5	2.84	74.18
M4	3.44	8.51	1.84	3.5	1.33	61.71
M5	3.69	9.53	1.53	4.5	0.73	64.57
M6	2.96	10.53	0.45	4.5	0.69	75.86
M7	5.08	7.43	1.47	5.0	0.75	68.53
M8	5.04	8.33	1.05	5.5	0.68	71.55
M9	4.37	9.43	0.6	5.5	0.62	75.43
M10*	3.0	9.80	0.8	5.5	0.55	79.04
	(3.20)	(9.86)	(0.86)	(4.7)	(0.54)	-
M11	9.6	10.3	3.3	3	5.98	-

*The parenthesis shows the predicted values.

at rotational speed of 100 rpm at 37° using distilled water as a dissolution media. The samples (5 ml) were withdrawn at predetermined time interval, filtered through a 0.45 μm membrane filter, diluted and assayed at 237 nm using a UV/Vis spectrophotometer (model U 2000, Hitachi, Tokyo)[15].

RESUTLS AND DISCUSSION

Lactose, starch, and physical blends of lactose and starch exhibited poor flow (Carr's index >26). Hence, modification is necessary to improve the flow. Wet granulation was adopted to improve the flow and compressibility. An ideal directly compressible adjuvant shall exhibit satisfactory flow to control weight of tablets and compressibility for adequate crushing strength.

Preparation of starch paste is an art as well as science. The characteristics of the starch paste depend on factors such as type of starch (maize, wheat and rice), the difference between gelatinization temperature, heating time and temperature, etc. In the present investigation, starch paste was prepared at peak gelatinization temperature of corn starch. Compared to the conventional method of manufacturing the starch paste, relatively longer heating time was tried in the present study to facilitate leaching of amylopectin, a constituent of starch that confers binding. Later in present study, a comparison was made between the classical method of the preparation for starch paste and the method adopted.

One of the objectives of the present study was to develop an economical adjuvant. To investigate the maximum amount of starch that can be incorporated, different blends of lactose and starch (lactose/starch ratio; 70:30, 50:50 and 30:70) were granulated with 5% starch paste (100 ml). Batches containing lactose/starch ratio (50:50 and 70:30) exhibited satisfactory characteristics (such as % fines (<7%) and Carr's index (<15). But, the tablets exhibited friability greater than 2% and crushing strength equal to 3 kg.

To augment binding and to reduce the friability of the granules, lactose/starch blends (50:50 and 70:30) was granulated with higher strength of starch paste (10%). The results revealed that on increasing the concentration of starch from 5 to 10%, the friability (< 2%) and % fine (< 5%) reduced. The crushing strength of the compact increased to 5 kg. The batch containing lactose/starch ratio 30:70 exhibited poor crushing strength and higher friability. This might be due to the poor bonding capacity of the starch, which undergoes elastic deformation. A 3^2 full factorial design was adopted (see Table 1).

One of the significant factors that affect powder flow is fines. Higher amount of fines (>10-20%), might affect the flow of the excipient especially when it is mixed with poorly flowable drug candidate. An arbitrary value of % fines less than 10% was kept as a selection criterion. Lower values of fine was exhibited by batches containing high level of X_2 (batch M3, M6 and M9) at all the levels of X_1 (-1, 0, 1), (see

TABLE 3: REGRESSION OUTPUT FOR DEPENDENT VARIABLES.

Coefficient	b_0	b_1	b_2	b_3	b_4	b_5	R^2
Fines (%)	3.363	-0.048	-0.718	1.515	*	*	0.75
	(3.427)	(-0.048)	(-0.718)	(1.515)	(-0.095)	(0.603)	(0.90)
Carr's Index	9.523	1.026	0.548	-2.153	*	*	0.86
(%)	(9.322)	(1.026)	(0.548)	(-2.153)	(0.302)	(0.683)	(0.96)
Granular	1.300	-0.286	-0.655	*	*	*	0.90
Friability (%)	(1.441)	(-0.286)	(-0.655)	(0.053)	(-0.252)	(0.200)	(0.98)
Crushing	3.0722	1.833	0.5	*	*	*	0.92
strength (Kg)	(4.277)	(1.833)	(0.5)	(-0.667)	(-0.166)	(-0.375)	(0.98)
Friability	0.917	-3.027	-1.397	2.793	*	1.87	0.96
(%)	(0.914)	(-3.027)	(-1.397)	(2.793)	(0.003)	(1.87)	(0.97)

The parenthesis represents values of coefficient for full model ($Y=b_0+b_1X_1+b_2X_2+b_3X_1^2+b_4X_2^2+b_5X_1X_2$), R^2 is the square of the multiple linear regression coefficient, and *indicates that the regression coefficient is not significant at (α=0.05).

Table 2). The slight increase in the value of % fines was shown by the batches M7-M9. This might be due high viscosity of the binder solution, which does not distribute well in the powder blend. The results of multiple regression analysis suggest that the factor X_2 exhibited significant impact on the percentage fines (Table 3). Hence, high level of the factor X_2 should be selected for the minimizing %fines.

The value of Carr's index between 5 and 15 indicates excellent flow[16]. All the batches exhibited excellent flow (Table 2). The probable reason might be the uniformity in size of the granules. From the results of multiple regression analysis, it can be concluded that that factor X_1 has more significant effect on Carr's index than factor X_2 (Table 3).

Higher granular friability may lead to fragmentation of granules during handling in a tablet department, e.g. dry blending of disintegrant, glidant or lubricant. Granules containing higher % of fines will show poor flow, which will result in weight variation. An arbitrary value of 1% for the granular friability was kept as a selection criterion. Batches M3, M6 and M9 met the selection criterion. Highest value of granular friability was observed in batches having low level of either of the independent variable. Probable reason is weak bonding between the particles in the granules. The batches containing high level of factor X_1 contained higher amount of water soluble component and lower amount of insoluble component (starch) which also might have affect the formation of stronger bonds resulting from fusion or recrystallization of particles and curing of the binder[17]. High level of X_2 gave low value of granular friability at all the levels of X_1 (fig. 1). The results of multiple regression analysis support these findings. From the results, it can be concluded that both the variables have negative effect on the granular friability (Table 3). Factor X_2 has more significant effect than that by factor X_1.

For the selection of batches crushing strength greater than 5 kg was kept as a criterion. Batches M6-M9 met the criterion (Table 2). Tablets containing high level of X_1 resulted in higher crushing strength in their respective treatment group (fig. 1). The probable reason might be the presence of higher amount of lactose, which deforms by brittle fracture. It is well known that starch undergoes elastic deformation. As anticipated, increase in binder strength resulted in high crushing strength. From the results of multiple regression analysis, it can be concluded that X_1 has more significant effect on crushing strength than factor X_2.

Tablet friability less than 1% was kept as a selection

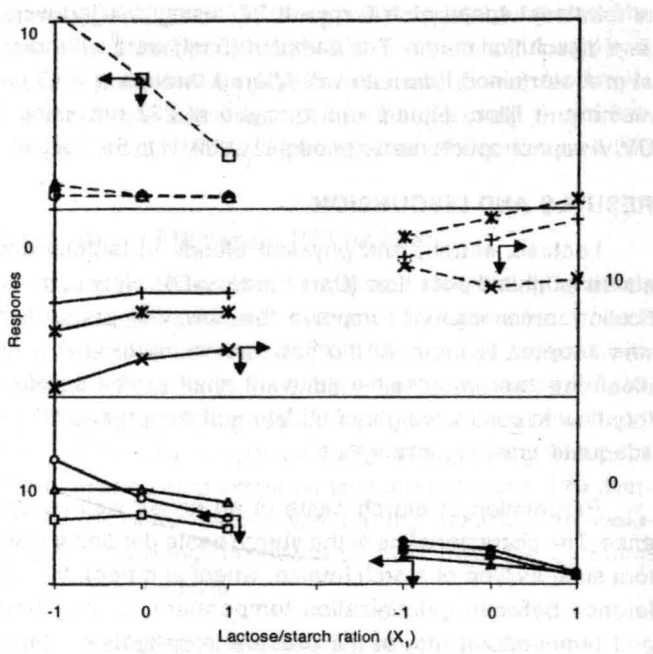

Fig. 1: Effect of lactose: starch ratio on various parameters.

X_2 (6, 10 and 14%) for; % Fines (-○-), (-□-), (-△-); Carr's index (---x---), (---+---), (---✱---); granular friability (-●-), (-■-), (-▲-); crushing strength (-x-), (-✱-), (-+-); and friability (---+---), (---△---), and (---○---), respectively.

criterion. Batches M1-M4 failed to meet the criterion (Table 2). This might be due to either low amount of binder and/or due to higher amount of starch. From the results of multiple regression analysis, it can be concluded that both the variables have negative effect. An ideal batch is one which satisfies all the set requirements simultaneously. In order to identify an ideal batch further data treatment was given

A contour plot was generated from data obtained from the refined models. An area was identified in the contour plot, which shows acceptable compositions of factor X_1 and X_2. A checkpoint (batch M10) having co-ordinates, X_1= 0.4 and X_2= 0.5 was prepared to validate the evolved model. The result showed insignificant difference between the predicted and experimental values of dependent variables for batch M10 (Table 2). It can be concluded that the evolved models can adequately predict the value of the dependent variables.

To select the best batch among ten batches prepared (batch M1-M10), a composite index was calculated[18]. In composite index maximum score can be 100. All the dependent variables were assigned equal score of 20. The batch M10

obtained highest score of 79. Hence, it may be ranked as the best batch.

Batch M11 was prepared using the starch paste prepared by conventional method of preparation of starch paste. From the comparative results of batch M10 and M11 (Table 2), it is quite clear that batch M10 is superior with respect to all the parameters than batch M11. The most significant effect was observed on % fines, granular friability, crushing strength and friability. It is well known that all the four parameters are greatly influenced by the cohesiveness or the binding ability of granulating agent. Starch is composed of amylose (20-30%) and amylopectin (70-80%). It is postulated that amylopectin is responsible for binding activity[19]. Prolonged heating might have caused breakdown of starch and liberation of amylose and amylopectin. Based on the results of DSC study, Stevens and Elton reported that peak gelatinization temperature of cornstarch is 78-79° [20]. Hence, in present study, 80° was selected as a heating temperature. Heating time was 15 min to facilitate breakdown of starch. Starch paste prepared by conventional method was dull in appearance whereas the starch paste prepared at 80° (batch M10) was having smooth and lustrous surface. The study underlines the importance of heating temperature and time. Batch M10 was characterized further.

Geometric mean granule size is a best parameter for the evaluation of tablet hardness and friability[21]. Mean particle size distribution of batch M10 is shown in fig. 2. The mean particle size of granules of batch M10 was 223 μm. The granular friability index near to one and friability rate constant near zero indicates the toughness of the granules. After 90 min in a friabilator, granules of batch M10 exhibited friability index and friability rate constant equal to 0.0092 and 0.00091 respectively. From this data, it can be assumed that the granules are not too friable and might not break during the transportation or mixing.

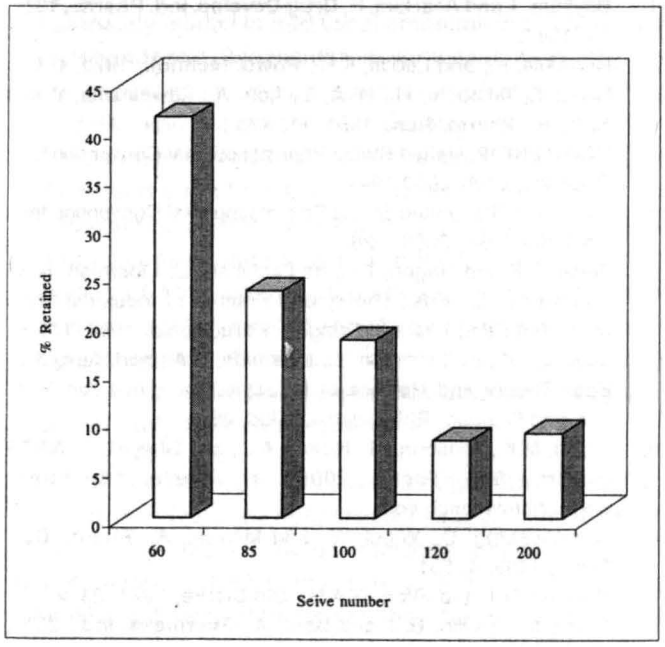

Fig. 2: Particle size distribution of Batch M10. (-□-) Batch M10.

The packability of agglomerates of batch M10 was ascertained by comparing the constants a, b and k in Kawakita's and Kuno's equations, respectively. The constant "a" represents the proportion of consolidation as closest packing is attained. The reciprocal of "b" and "k" represent the packing velocity. The constant "a" for the batch M10 was smaller (0.275) than for the untreated lactose/starch blend (0.382). The result indicates that the agglomerates of batch M10 showed good packing even without tapping. The reciprocal for "b" for batch M10 and physical mixture of lactose/starch blend was 0.0774 and 0.0765 respectively. The large value of b for the agglomerates of batch M10 proved that the packing velocity of the agglomerates of batch M10 faster than that of the lactose: starch physical blend (fig. 3). The "k" in Kuno's equation for batch M10 and physical mixture of lactose and starch was 0.00259 and 0.00309, respectively. The smaller value of "k" in the Kuno's equation supports the above findings. The slow packing velocity corresponds with proportion of the consolidation of the powder bed per tap. The agglomerates of batch M10 showed improved compression property compared to lactose, microcrystalline cellulose blend due to improved packability.

Tablets containing 10, 20 and 30% acetaminophen, a poorly compressible model drug, exhibited satisfactory characteristics. All the batches exhibited crushing strength greater than 3.5 kg, friability less than 0.95%. From fig 4, it can be concluded that as the percentage of acetaminophen increased the crushing strength of tablets decreased. It is concluded that batch M10 exhibited satisfactory dilution potential. The tablets prepared from granules of batch M10 with model drug diltiazem HCl exhibited crushing strength, friability and disintegration time 5.5 kg, 0.5% and 4 min, respectively. Ninety five percent of the drug was released in 15 min due to rapid disintegration of the tablets.

The present study demonstrates the use of experimental design for the preparation of directly compressible excipient. The results of multiple regression analysis can be

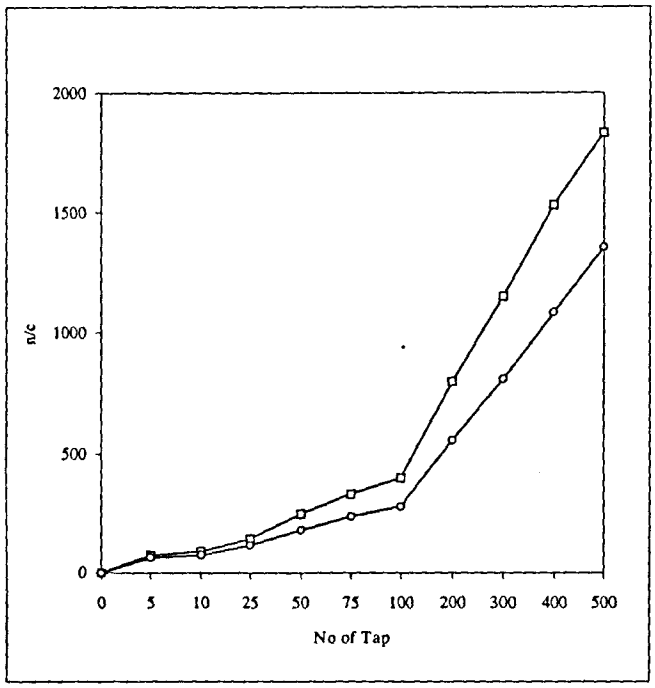

Fig. 3: Comparative Kawakita plot for batch M10.

(-□-) Batch M10, (-○-) physical mixture of lactose and starch.

used to predict the effect of independent variables on the dependent variables. As indicated by the magnitude of the regression coefficients, the lactose/starch ratio (X_1) has greatest effect on the crushing strength, granular friability, Carr's index and friability of the tablets. As the lactose/starch ratio increased Carr's index and crushing strength of the tablets were increased while tablet friability decreased, whereas, percentage of starch paste had inverse effect on granular friability and % friability of the tablets. This might be due to increased interparticulate adhesion between lactose and starch particles with higher proportion of binder.

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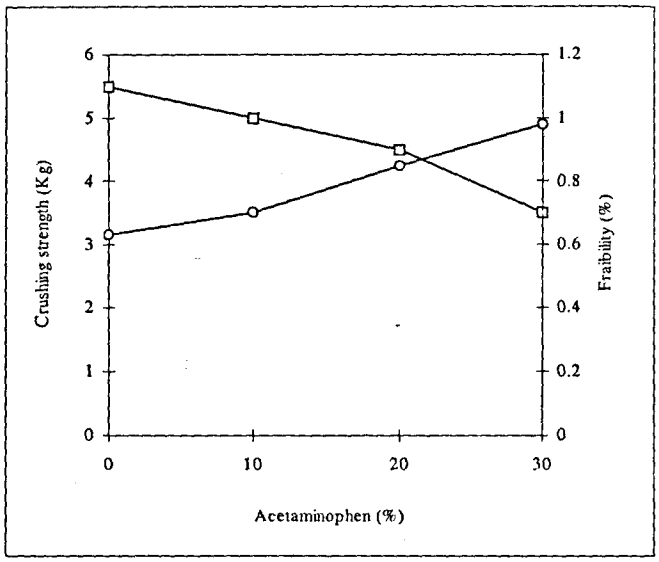

Fig. 4: Effect of acetaminophen on crushing strength and % friability.

(-□-) Crushing strength (kg) and (-○-) % friability.

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