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Research article

DEVELOPMENT OF DIRECTLY COMPRESSIBLE CO-PROCESSED EXCIPIENT FOR DISPERSIBLE TABLETS USING 3^2 FULL FACTORIAL DESIGN

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ABSTRACT

The purpose of the present research was to prepare and evaluate mannitol and cellulose based, directly compressible excipient using freeze-thawing technique. The mannitol to cellulose ratio (50:50, 60:40, and 70:30) and the rotation speed of propeller stirrer (200, 600, and 1000 rpm) were selected as independent variables in a 3^2 full factorial design. Water acted as a good medium for mannitol as well as a bridging liquid for agglomeration of mannitol with cellulose. The agglomerates were evaluated for percentage fines and carr's index. Tablets were prepared on a rotary tablet press, and they were evaluated for friability, tensile strength, water absorption ratio, and disintegration time. Multiple linear regression analysis was carried out to evolve full and reduce models. The use of composite index was demonstrated for the selection of an appropriate batch. The optimized batch was characterized by different scanning calorimetry (DSC), scanning electron microscopy, Fourier Transform Infrared (FTIR) Spectral Study, granular friability, Kawakita's equation, Kuno's equation and Heckle equation. The results of dilution potential study reveal that up to 30% nimesulide, a poorly compressible drug and 50% metformin, a hygroscopic drug, can be incorporated in the co-crystallized product. The product was less sensitive to lubricant in lubricant sensitivity test. In conclusion, the properties of agglomerated product, such as flowability, compactibility, and dissolution rate were improved profoundly using the developed technique resulting in successful direct tableting without need to additional process of physical blending of agglomerates.

Keywords: Co-processing, Freeze-thawing technique, Heckel plot, Kawakita's and Kuno's equation, Factorial design.

INTRODUCTION

Tablets can be manufactured by wet granulation, dry granulation, or direct compression. Most of the pharmaceutical manufacturers are opting for direct compression tableting due to its require fewer processing steps, simplified validation, elimination of heat and moisture, economy, and improved drug stability compared with wet granulation

technique. Dry granulation requires control of more processing variables than the direct compression. Reproducibility of the product is difficult to achieve in dry granulation. Hence, the current trend in the pharmaceutical industry is to adopt direct compression technology.

Although simple in terms of unit process involved, the direct compression process is highly influenced by powder characteristics such flowability, compressibility and dilution potential. The other attributes that directly compressible excipients should possess are summarized by Jivraj et al[1]. No single material likely to exhibit all the ideal characteristics. The physico-mechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machine ability even in high speed tableting machines with reduced dwell times[2]. Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials and new combination of existing materials[3]. New combinations of existing excipients are an interesting option for improving excipients functionality because all formulations contain multiple excipients. A much broader platform for the manipulation of excipient functionality is provided by co-processing or particle engineering of two or more excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual[4].

Co-processing excipients leads to the formation of excipients that granulates with superior properties compared with physical mixtures of components or individual components. Usually a combination of plastic and brittle materials is used for co-processing. This combination prevents storage of too much elastic energy during the compression, which results in a small amount of stress relaxation and a reduced tendency of capping and lamination thereby optimum tableting performance[5]. Cellulose is well known as a tablet diluent, binder and disintegrant. Cellulose exhibits disintegration property due to capillary action; it has a self-lubricating quality and thus, it requires less lubrication than other excipients. In addition, it exhibits inherent compatibility because of plastic deformation and limited elastic recovery. One of the few problems associated with cellulose is its very poor flowability, which can lead to

variability of the drug content in the finished dosage form[6]. Hence, it needs to be modified into large particle with improved flow properties. Mannitol exhibits low moldability, less sensitivity to humidity, good aqueous solubility, negative heat of solution and good wetting properties[7]. In this investigation mannitol was combined with highly compressible cellulose which has good wicking and absorbing capacity. These attributes may improve the binding of the tablet, increase the water uptake and thereby decrease the disintegration time of the tablets. In the present investigation mannitol combined with cellulose and it is used in formulation of Nimesulide and Metformin HCl dispersible tablets.

Nearly all excipients for direct compression are manufactured by granulation, agglomeration, co-crystallization, or spray-drying. Spray-drying has been used commercially to manufacture excipients with good functionality, but it can not be adopted at most pharmaceutical companies because it is not cost-effective compared with classical wet granulation, high capital investment, validation of many process variables, low percentage yield, space requirement in a factory etc. On the other hand, freeze-thawing (spherical crystallization) is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactibility of the excipients[8,9]. Freeze-thawing technique has its own merits, and hence, this method was adopted in this study. Cost-containment efforts have made a significant impact on formulation development in recent years.

MATERIALS AND METHODS

Mannitol was obtained from Lesar Chemicals, Ahmedabad. Cellulose and crospovidone were obtained from Acs Chemicals and Cadila Healthcare Ltd., Ahmedabad, respectively. The drugs Nimesulide, Aceclofenac and Metformin HCl were obtained as gift sample from Ipca Laboratories Ltd., Mumbai and Sun Pharmaceutical Pvt. Ltd., Vadodra respectively. Magnesium stearate and Talc were used as received from Apex chemicals, Ahmedabad.

Freeze-thawing method for co-processed agglomerates[10]

A 3^2 full factorial design was employed to study the effect of mannitol/cellulose ratio (X_1) and the rotating speed of propeller stirrer (X_2) at three different levels i.e. low (-1), medium (0) and high (+1). Semisolid products consisting various amount of cellulose (<74 µm particle size) in 50 ml distilled water

was stored at room temperature for 30 min for promoting wetting of the cellulose particles. Varying amount of mannitol (<125 µm particle size) was dissolved in 50 ml distilled water at 80°C temperature on water bath and the cellulose dispersion were mixed using a propeller stirrer (Table 1). One gram hydroxy propyl cellulose (HPC) uniformly dissolved in dispersion an ambient temperature and was stirred under varying stirring speed (200, 600, 1000 rpm) for 1 h. The dispersion was cooled to 10ºC using a cold water bath. After about 20 min the dispersion was placed in a deep-freezer (-12°C) for 18 hrs to promote crystallization. The frozen product was thawed by placing it in a water bath maintained at 20°C, until the ice melted. The mannitol-cellulose agglomerates were separated using vacuum filtration and partially dried under vacuum. Then the wet coherent mass was passed through a 44 mesh. The wet agglomerates were dried in a hot air oven at 60°C for 90 min. The dried agglomerates of 44/200 mesh fraction were kept in an airtight container till further use. A checkpoint batch (X_1 = 0.5, X_2 = 0.5) was also prepared by the same method.

Table 1. Composition of batches using 3^2 full factorial design layout

Batch code	Variables levels in coded form		Actual values of variables	
	Mannitol:cellulose ratio (X_1)	**Rotating speed (X_2)**	**Mannitol:cellulose ratio (X_1)**	**Stirring speed (X_2)**
S1	-1	-1	50:50	200
S2	-1	0	50:50	600
S3	-1	+1	50:50	1000
S4	0	-1	60:40	200
S5	0	0	60:40	600
S6	0	+1	60:40	1000
S7	+1	-1	70:30	200
S8	+1	0	70:30	600
S9	+1	+1	70:30	1000
S10*	0.5	0.5	65:35	800

Variable	Level		
	Low (-1)	**Medium (0)**	**High (+1)**
Mannitol: Cellulose Ratio (X_1)	50:50	60:40	70:30
Rotation Speed (X_2)	200	600	1000

* is the check point batch, All the batches were stirred for 1 hr and freeze at (-12°) C for 18 hrs.
All the batches were contains 1 gm Hydroxyproply cellulose

Evaluation of agglomerates

Scanning electron microscopy (SEM) study

The shape and surface topography of the cellulose, mannitol, and co-crystallized agglomerates of batch S5 were observed by scanning electron microscopy (JEM-6400, Jeol Ltd, Japan) after coating with gold.

Fourier transform infrared (FTIR) spectral study

Fourier transform infrared (FTIR) spectral data were taken on a Shimadzu (model FTIR-8300, Tokyo, Japan) instrument to find out the chemical stability of the excipients. FTIR spectra of the pure mannitol, cellulose powder, co-processed agglomerates of batch S5, and physical mixture of mannitol & cellulose in the same ratio were obtained. All the samples were crushed with potassium bromide to get pellets at 1 ton/cm^2. Spectral scanning was done in the range between 4000-400 cm^{-1}.

Differential scanning calorimetry study

Different scanning calorimetry (DSC) was performed on pure mannitol, cellulose, co-crystallized agglomerates of batch S5, and physical mixture of mannitol and cellulose (Shimadzu DSC-60, Tokyo Japan). Approximately 20 mg of sample was weighed into a 40 µL aluminum pan and compressed in a dry air atmosphere. Pans were then sealed hermetically and transferred into the DSC cell. Two different methods were applied. First, all formulations were scanned with ramp rate of 10˚C min^{-1} from 50˚C-300˚C to reveal potential glass transitions, melting events, or re-crystallization. A lower ramp rate (2.5˚C min^{-1}) was used for samples showing inconclusive results at fast ramp rates.

Percentage of fines in agglomerated product

The percentage fine is defined as the percentage of the agglomerates passed through 200 # (74 µm). The agglomerates were agitated on a rotap sieve shaker (International Combustion Ltd., London, U.K.) on 200 # for 5 min for finding percentage fines. The 44/200 (350/74 µm) sieve fraction was used for further evaluation.

Carr's index

The bulk density was the quotient of weight to the volume of the sample. Tapped density was determined as the quotient of weight of the sample to the volume after tapping a measuring cylinder for 500 times from a height of 2 inch. The Carr's index (percentage compressibility) was calculated as one hundred times the ratio of the difference between tapped density and bulk density to the tapped density[10].

Manufacturing of tablets

The agglomerates (97%) of batches S1-S10 were blended with 2% talc for 5 min and with 1% magnesium stearate

for 2 min. Tablets were compressed using Rimek ten station rotary tablet machine using 10-mm diameter flat-faced punches and die (Cadmach Machinery Private Ltd., Ahmedabad). The average weight of the tablet was 300 mg. The minimum distance between the upper and lower punch was between 0.30 and 0.32 cm during preparation of tablets.

Evaluation of tablets

Tensile strength

The dimensions of tablets were measured by using a micrometer. The crushing strength was determined after 24 hr (time for stress relaxation) of compression, by using a Monsanto hardness tester (Shital Scientific Industries, Bombay, India). From the values of diameter (D, cm), thickness (L, cm), and crushing strength (P, Kg), the tensile strength (T) (MPa) of the tablets was calculated by using Equation 1[12].

$$T = \left(\frac{0.0624 \times P}{D \times L} \right) \ldots\ldots (1)$$

Friability

Friability was evaluated as the percentage weight loss of 20 tablets tumbled in a friabilator (model EF2, Electrolab, India) for 4 min at 25 rpm. The tablets then were dedusted, and the loss in weight caused by fracture or abrasion was recorded as percentage friability[13].

Disintegration time

Disintegration test (model ED2, Electrolab, India) was performed on six tablets at 37ºC in 900 ml of distilled water in accordance with USP 24[14].

Water absorption ratio (%)

A piece of tissue paper folded twice was placed in a small petridish (Internal Diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the following Equation 2.

Water absorption ration (R) =

$$\left(\frac{W_a - W_b}{W_b} \right) \times 1\ 00 \ \ldots\ldots\ldots (2)$$

Where, W_b is the weight of the tablet before water absorption and W_a is the weight of the tablet after water absorption.

Calculation of composite index

On completion of the individual experiments, a weighted composite index was used to designate a single score utilizing two responses, i.e., Carr's index (%), and Friability (%). As the relative contribution of each individual constraint to the "true" composite score was unknown, a decision was made to assign an arbitrary value of one-half to each of the two response variables[15]. The empirical composite index was

devised to yield a score 100 for an optimum result for each of the two responses and each formulation result was transformed to a value between 0 and 50. For tensile strength, highest value (1.370) was assigned a score equal to 50, and lowest value (0.879) was assigned zero score. For friability (%), lowest value (0.339) was assigned to 50 score and the highest value (1.283) was assigned to zero score. The batch having the highest composite index would be considered as a batch fulfilling the desired criteria.

The raw data transformations whereas follows:

Value of tensile strength of friability =

$$= \frac{Yi - Ymin}{Ymax - Ymin} \times 50$$

Where Yi is the experimental value of individual response variable, Ymax and Ymin are maximum and minimum values of individual response variable, respectively.

Composite Index = Transformed value of Carr's Index + Transformed value of Friability (%)

Particle size distribution

Particle size distribution was performed on random samples of batch S5 using a nest of standard sieves (30, 44, 60, 85, 100, 120 and 200 #). The 30, 44, 60, 85, 100, 120 and 120 # have 590-, 350-, 250-, 177-, 149-, 125-, and 74- µm opening. The sieves were agitated on a rotap sieve shaker (International Combustion Ltd., London, U.K.) for 10 min. From the percentage weight of agglomerates retained on each sieve, the mean agglomerates diameter was calculated[16].

Granular friability index

Agglomerates of batch S5 (10 gm) were rotated for 5, 10, 20, 30, 40, 50, and 60 min at 25 rpm in a Roche friabilator (model EF2, Electrolab, India). The samples were evaluated for the particle size distribution, and the mean particle size was calculated. The friability index (FI) was calculated as the ratio of the mean particle size of the friabilator-treated agglomerates to the mean particle size of the untreated agglomerates (initial). The negative natural logarithm of the friability index of the agglomerates was plotted against the time of rotation in a friabilator. From the value of slope of the line, a friability rate constant was obtained[17].

Kawakita's and kuno's equation

The packability was evaluated by tapping the agglomerates in a measuring cylinder. The data were analyzed by using Kawakita's[18] and Kuno's[19] Equation 3 and 4, respectively.

$$\frac{n}{C} = \frac{1}{ab} + \frac{n}{a}$$

$$a = \frac{V_o - V_{inf}}{V_o},\ C = \frac{V_o - V_n}{V_o} \quad \text{.....(3)}$$

Where "a" and "b" are the constant, n is the tap number, Vo, Vn, and Vinf are the powder bed volumes at initial, after *n*th tapping and at equilibrium state, respectively.

$$\rho_f - \rho_n = (\rho_f - \rho_o)e^{(-kn)} \quad \ldots\ldots\ldots (4)$$

Where ρ_o, ρ_n, and ρ_f, are the apparent densities at initial state, after *n*th tapping (5, 10,15, 20, 25, 50, 75, 100, 200, 300, and 400) and equilibrium (500^{th} tap) respectively, and k is a constant.

Heckel analysis

The compressibility behavior of the agglomerates of batch S5, untreated mannitol, cellulose, and physical mixture having same composition were studied using Heckel equation[20,21]. Agglomerates-powder (500±5 mg) was compressed in a hydraulic press (SSP-16 A, Shimadzu Corporation, Japan) using a 13-mm flat-faced punch and matching die at pressures of 1, 2, 3, 4, 5 and 6 tons for 1 min. The compacts were stored over silica gel for 24 hr to allow elastic recovery, hardening and prevent falsely low yield values before evaluations. The weight, diameter and thickness of the compacts were determined. The data were processed using Heckel equation. The mean yield pressure (Py) from the reciprocal of k, was obtained by regression analysis of the linear portion of the plot.

$$\ln\left(\frac{1}{1-D}\right) = Pk + A \quad \ldots\ldots\ldots (5)$$

Where, k and A are constant, D and P are the packing fraction and pressure respectively.

Effect of lubricant

Agglomerates of batch S5 and magnesium stearate were mixed in 99:1 proportion and compressed into tablets (Table 6). The lubricant sensitivity ratio was evaluated as the ratio between difference in tensile strength of an unlubricated tablet and a lubricated tablet to the tensile strength of an unlubricated tablet[22].

Dilution potential study

Dilution potential is the amount of poorly compressible drug that can be satisfactorily compressed into a tablet with a directly compressible excipient. Nimesulide was taken as a model drug for the evaluation of dilution potential of the batch S5 (Table 7).

Moisture uptake

A 5-gm sample from batch S5 was spread uniformly in a 5 cm diameter petridish, and the dish was stored at 75% relative humidity at 45°C in a dessicator. The percentage increase in weight was noted after 24 hrs.

Formulation and evaluation of tablets containing model drug

To demonstrate the compressibility and the tableting performance of the developed multi-purpose excipient, three model drugs were selected. Nimesulide is a medium-dose, poorly compressible drug. Metformin HCl is a high dose, poorly flowing and hygroscopic drug. Aceclofenac is a low dose, crystalline drug. Agglomerates of batch S5 were mixed with the model drug, crospovidone, sodium saccharin, and talc for 5 min. The blend was mixed with magnesium stearate for 2 min. The final mixture was directly tableted (300 mg) on a Rimek ten station rotary tablet machine using 10 mm diameter flat-faced punches (Cadmach Machinery Private Ltd., Ahmedabad). The tablets were evaluated for weight variation, friability, tensile strength, disintegration time, in-vitro drug release (Table 8).

***In-vitro* drug release study**

The *In-vitro* drug release study of Nimesulide tablets was performed using a USP apparatus (model TDT-60T, Electrolab) fitted with baskets (50 rpm) at 37±0.5ºC using phosphate buffer (pH–7.4) as a dissolution medium. At a predetermined time interval, 10 ml samples were withdrawn, filtered through a 0.45 µm membrane filter, and assayed at 394 nm by using UV/Vis Spectrophotometer (Shimadzu 1601, Tokyo, Japan) to determine the percentage drug released. The same volume (10 ml) of fresh dissolution medium was replenished immediately after the sample was withdrawn[23].

The *in vitro* drug release study of Metformin HCl tablet was performed using a USP apparatus fitted with paddles (100 rpm) at 37±0.5ºC using phosphate buffer (pH–6.8) as a dissolution medium. At a predetermined time interval, 10 ml samples were withdrawn, filtered through a 0.45 µm membrane filter, and assayed at 234 nm by using UV/Vis Spectrophotometer to determine the percentage drug released[24].

Short-term stability study

The formulations containing Nimesulide and Metformin HCl were subjected to a short-term stability study. The tablets were kept in a closed glass container for 3 months at 45°C at 75% relative humidity. The tablets then were evaluated for the pattern of drug release.

RESULTS AND DISCUSSION

Morphology of agglomerates

An examination of the SEM shows the morphology of the starting material (Fig. 1a & 1b). SEMs of the untreated cellulose and the mannitol show no evidence of porosity, whereas the crystallized agglomerated particles (Fig 1c) indicated evidence of porosity. The untreated cellulose and mannitol particle were slightly fibrous and plate like in

appearance, respectively, whereas co-crystallized agglomerates were random in size and nearly spherical in shape. The particles of mannitol and cellulose were held together in the agglomerates probably because of adhesive quality of HPC. The particles are held together by HPC bridges in wet state. On drying, the liquid bridges are converted to solid bridge.

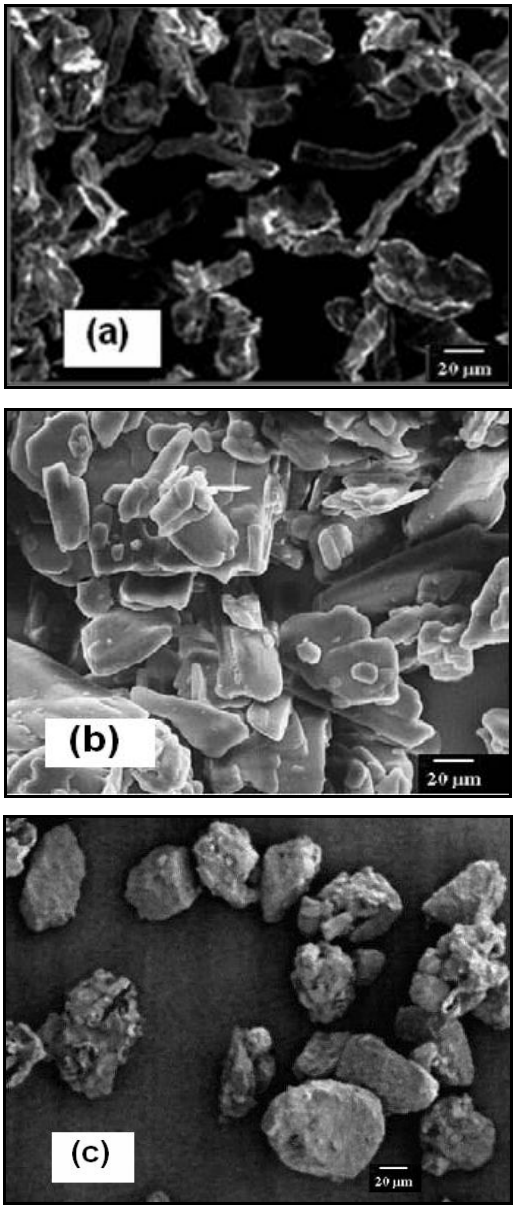

Fig. 1 : SEM photograph of (a) Cellulose (b) Mannitol and (c) Co-crystallized agglomerate of batch S5 (Under original magnification x400)

Thermal analysis

DSC analysis indicated that melting endotherm peak of mannitol at 170.20°and cellulose peak at 91.08° are intact in co-crystallized agglomerates and physical mixture (Figure 2). Co-crystallized agglomerates shows heat energy value of -295.16 mJ or -58.97 mJ but physical mixture shown a value of -445.20 mJ or -74.70 mJ indicating that amorphization has occurred in the co-crystallized agglomerates.

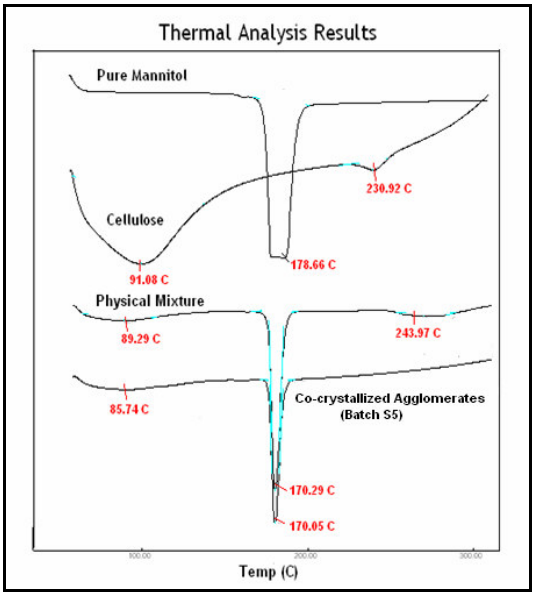

Fig. 2 : DSC Thermograms of (a) Pure Mannitol, (b) Cellulose powder, (c) physical mixture of mannitol & cellulose and, (d) Co-crystallized agglomerate (Batch S5).

FT-IR study

FTIR studies as displayed in Figure 3, the prominent peaks of mannitol at 3279, 2359, 2059 and 1420 cm^{-1} present in both co-processed agglomerates (batch S10) and physical mixture indicated that there was no interaction

between the two excipients. Characteristic peaks of cellulose at 3427 cm^{-1} (O-H stretching vibration band), 1429 cm^{-1} (intramolecular hydrogen bonds at the C_6 group and O-H in plane bending vibration), and 883 cm^{-1} (antisymmetric out-of-phase stretching vibration) present in both batch S10 and physical mixture indicated chemical compatibility in co-processed agglomerates. The absence of chemical changes helps to reduce a company's regulatory concerns during the development phase.

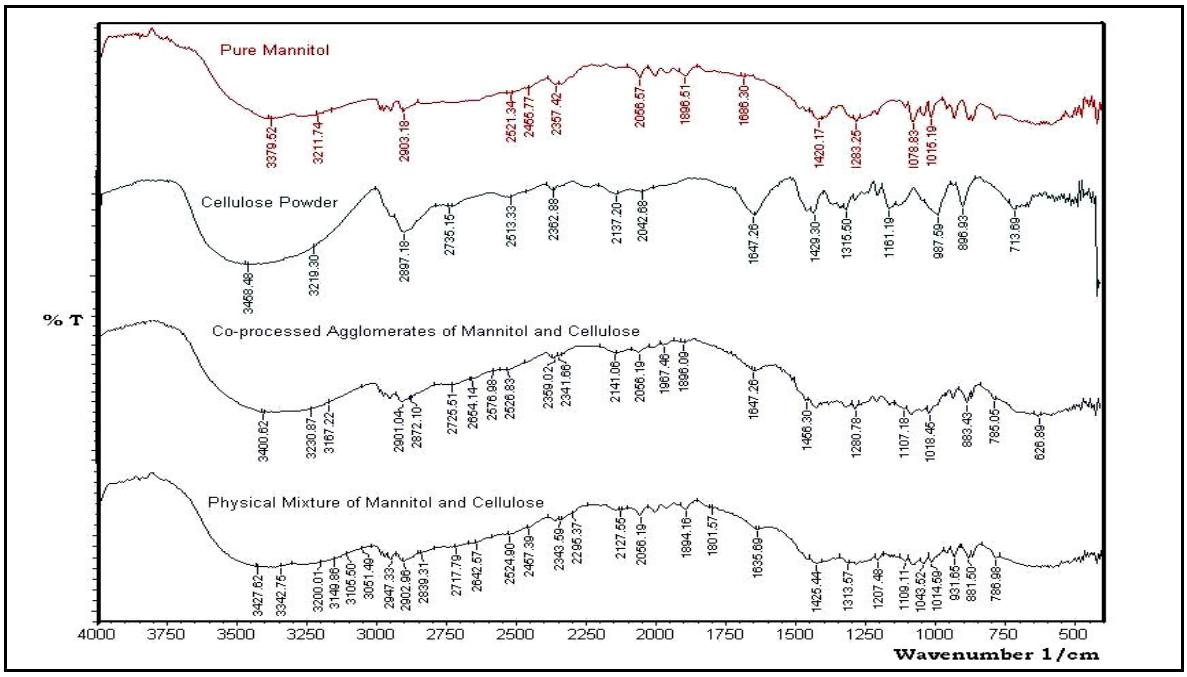

Fig. 3 : FTIR spectra of (a) Pure mannitol, (b) Cellulose powder, (c) Co-crystallized agglomerates of batch S5, and (d) Physical mixture of mannitol and cellulose

Besides the other factors, the ratio of the mannitol to cellulose powder and rotating speed of propeller stirrer determines the strength of agglomerates. Hence, ten batches (S1 to S10) were prepared and evaluated. The results are summarized in Table 2.

Percentage fines

It was arbitrarily decided to select batches that show percentage fines <20%. The percentage fines ranged from 9 to 49, indicating significant effect of the independent variables on the response. The batches (S4 – S6) containing 60 parts mannitol and 40 parts cellulose, showed a low percentage fines. The probable reason for superior performance of batches S4-S6 may be more uniform surface coverage of cellulose particle by mannitol. In case of mannitol:cellulose ratio the amount of mannitol was either decreased or increased the amount of percentage fines also increased due to insufficient

recovery of nuclei for development of co-crystallized agglomerates. The negative sign of its coefficients indicated that both the factor reduce the percentage fines (Table 3). It is well known that the rate of nucleation is dependent on agitation. In general, more number of nuclei will form under a strong agitated condition. At higher rotation speed (i.e. 200, 600, 1000 rpm) percentage fines was decreased due to more amounts of nuclei developed for co-processing of particles. It may be concluded that both the independent variables should be critically controlled to get the required % fines.

Carr's index

The value of Carr's index between 5-15 and 15-20 indicates excellent and good flowability, respectively. Although values greater than 21 indicate poor flow[25]. Agglomerates of batches S8 and S9 was found to be >20, indicating poor compression characteristics (Table 2). The unsatisfactory flow of batches S8 and S9 may be due to the fines greater than 20 percentages. The positive sign of its coefficients indicated that both the factor increase the Carr's index values and thus yield agglomerates with poor flow (Table 3). The results revealed that the quantity of cellulose was inversely proportional to Carr's index value.

Friability

The tablets of all batches exhibited friability <0.991 % except batch S1 (Table 2). The negative sign of its coefficients indicated that both the factor reduce the friability of tablets (Table 3). The results suggested that the ratio of mannitol:cellulose (60:40) exhibited lower friability as compared with other batches.

Tensile strength

Tensile strength >0.85 MPa was selected as the selection criterion for the formulations. All the batches exhibited satisfactory tensile strength (Table 2). As expected, tensile strength of the tablets increased with decreased cellulose amount in mannitol to cellulose ratio. The positive sign of its coefficients indicated that both the factor increase the tensile strength, it can be concluded that a medium to high level of both the variables should be selected.

Disintegration time and water

Absorption ratio

As per pharmacopoeia disintegration time of dispersible tablet should be <5 min. Here all the batches exhibited disintegration time below the stated limit. Hence, disintegration time was not used for optimization. The probable reasons for quicker disintegration may be attributed to the presence of superdisintegrant, i.e. crospovidone as

well as due to presence of adjuvant like cellule powder, which facilitates disintegration process. As per the results, it can be concluded that the amount of cellulose decreased the time required for disintegration of time was also decreased (Table 2). The negative sign of its coefficients indicated that both the factor reduce the disintegration time (Table 3).

Results of water absorption ratio revealed that as the amount of cellulose was decreased the percentage of water absorbed also decreased, because of cellulose which is absorbent. Results of water absorption ratio indicated that at lower stirring speed the % fines was higher, means less amount of cellulose co-crystallized with mannitol (Table 2). The negative sign of its coefficients indicated that both the factor reduce water absorption ratio, it can be concluded that at medium level of both the variables should be selected for further study.

Table 2 : Results of batch R1-R9 using A 3^2 full factorial design

Batch Code	Fines (%)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Friability (%)	Tensile Strength (MPa)	DT* (Sec)	WAR** (%)	Composite Index
S1	48.07	0.36	0.41	12.19	1.283	0.879	41	128.93	0
S2	31.18	0.30	0.35	14.28	0.911	0.932	32	125.85	25.09
S3	24.60	0.40	0.47	14.89	0.734	1.071	23	122.77	48.62
S4	11.69	0.27	0.32	15.62	0.653	1.190	34	121.1	65.03
S5	10.17	0.38	0.46	17.39	0.438	1.370	22	116.11	94.75
S6	9.60	0.39	0.48	18.75	0.342	1.260	16	115.66	88.63
S7	18.30	0.33	0.41	19.51	0.836	1.230	19	98.66	59.41
S8	20.56	0.28	0.36	22.22	0.612	1.190	18	90.9	67.21
S9	21.68	0.37	0.49	24.48	0.418	1.163	15	89.59	74.73
S10	9.98 (11.13)	0.25*	0.31*	19.35 (20.68)	0.339 (0.351)	1.282 (1.290)	18 (17.77)	101.43 (104.71)	91.03 (91.21)

The parentheses show predicted values of check point batch S10.
*DT : Disintegration time, WAR** : Water absorption ratio

The join effect of important variables was studied by using a composite index. The maximum possible value of composite index is 100. The batch S5 and S10 (check point batch) exhibited composite index 94.75 and 91.03, respectively (Table 3). The major differences in both batches are due to carr's index and tensile strength. Among all formulations batch S5 may be ranked as the best batch considering the highest tensile strength, moderate carr's index, and higher composite index. A diluent that contains low percentage fines can accommodate a higher percentage of drug, which is generally added in powder form in direct compression.

Table 3 : Multiple regression analysis for dependent variables

Parameters	Coefficient of regression parameters							
	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	Adjusted R^2	P
Fines (%)	10.47	-5.55	-5.36	15.24	0.02**	9.21	0.8766	0.0477
	(10.48)	(-5.55)	(-5.36)	(15.24)		(9.21)	(0.9075)	(0.006)
Carr's Index (%)	17.51	4.14	1.8	0.675	-0.39**	0.567	0.9938	0.0003
	(17.25)	(4.14)	(1.8)	(0.675)		(0.567)	(0.9905)	(0.0006)
Friability (%)	0.439	-0.17	-0.21	0.32	0.057**	0.032**	0.9528	0.0078
	(0.47)	(-0.17)	(-0.21)	(0.32)			(0.9465)	(0.0004)
Tensile Strength (MPa)	1.29	0.116	0.03	-0.19	-0.03**	-0.06**	0.8203	0.0001
	(1.27)	(0.116)	(0.03)	(-0.19)			(0.8395)	(0.021)
Water Absorption Ratio (%)	116.4	-16.4	-3.44	-8.17	1.83**	-0.72**	0.9923	0.0005
	(117.6)	(-16.4)	(-3.44)	(-8.17)			(0.9877)	(0.0001)
Disintegration Time (sec)	23.55	-7.33	-6.66	0.66**	0.66**	3.5	0.9109	0.0014
	(24.44)	(-7.33)	(-6.66)			(3.5)	(0.9422)	(0.0004)

Response (Y) = $b_0 + b_1X_1 + b_2X_2 + b_{11} X_1^2 + b_{22} X_2^2 + b_{12} X_1 X_2$

R^2 is the square of the multiple correlation coefficient, **Indicates that the regression coefficient is insignificant at α=0.05, *Values in parentheses are coefficient of the reduce model

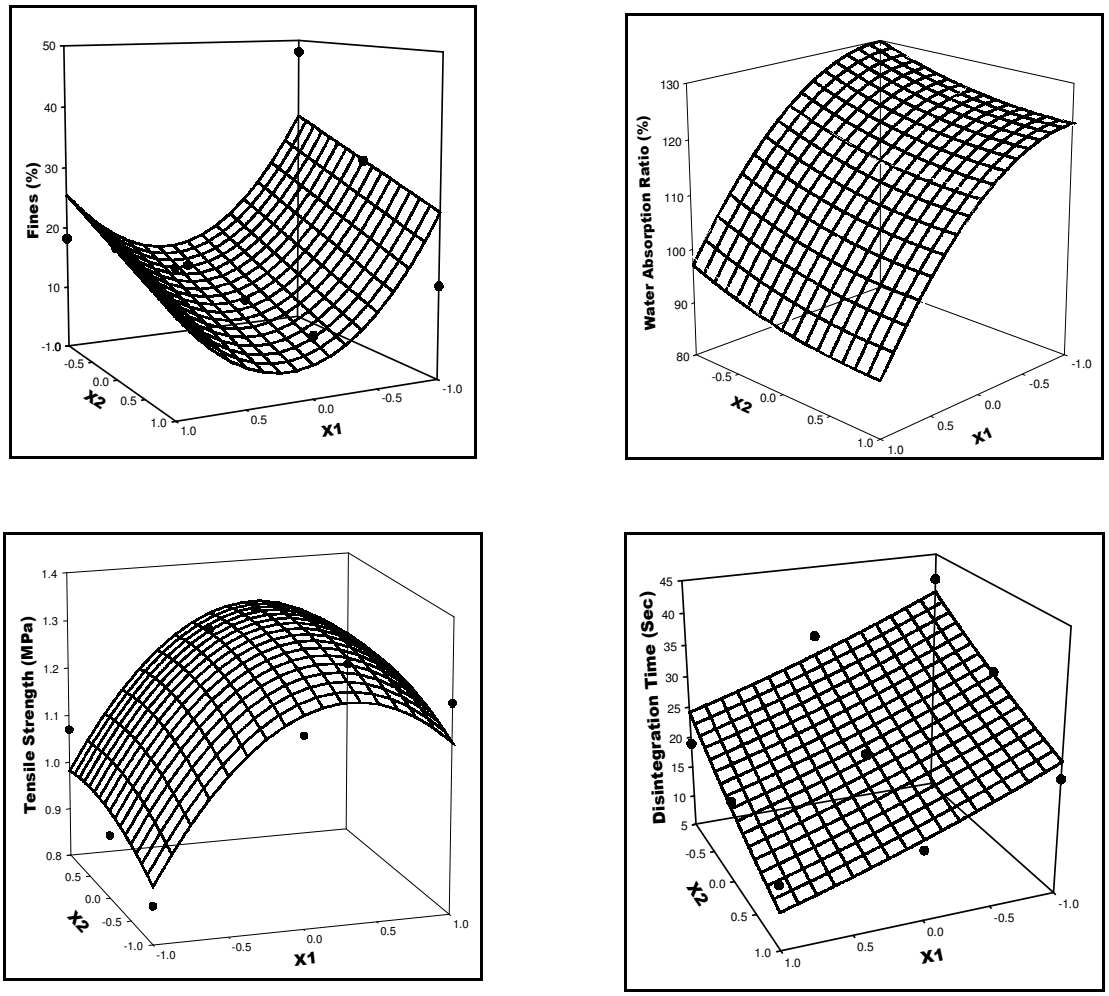

Fig. 4 : Effect of variables on the properties of co-crystallized agglomerates

To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) followed by Tukey test was performed using Sigma Stat software (Sigma Stat 2.03, SPSS, USA). Table 4 shows the results of ANOVA performed for the dependent variables using mannitol to cellulose ratio (X_1) as a factor and the stirring speed (X_2) as a variant. From these results, one can conclude that variable X_1 has significant effect on all the dependent variable except % fines. The variable X_2 exhibited insignificant effect on % fines and tensile strength among all dependent variables.

Characterization of agglomerates of batch S5

Particle size distribution

Particle size and particle size distribution of the samples have considerable impact on the flow properties of powder. Directly compressible excipient has to be mixed with powdered active medicament; hence, small granules are preferred. Figure 5 shows the particle size distribution of batch S5. Mean particle size of batch S5 was 189.09 ± 0.11 µm. About 88% particles are >120#, which may be the reason for the better flowability of agglomerates of batch S5 than that of the self powder or their physical blend.

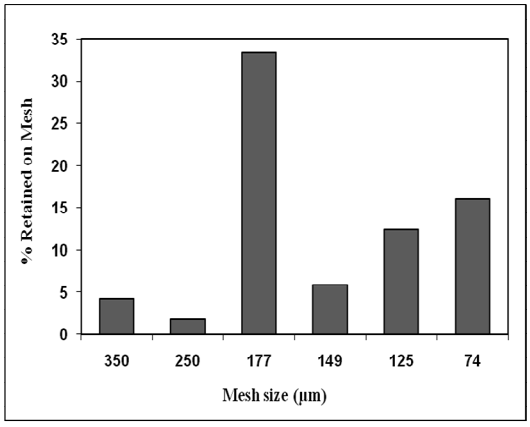

Fig. 5 : Particle size distribution of batch S5

Table 4 : Results of two way anova for measured response

(%) Fines					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Mannitol: Cellulose Ratio	2	649.74	324.873	3.283	0.143
Rotation Speed	2	172.59	86.296	0.872	0.485
Residual	4	395.80	98.952		
Total	8	1218.1	152.268		
Carr's index (%)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Mannitol: Cellulose Ratio	2	103.832	51.916	131.721	<0.001
Rotation Speed	2	19.744	9.872	25.048	0.005
Residual	4	1.577	0.394		
Total	8	125.152	15.644		

Friability (%)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Mannitol: Cellulose Ratio	2	0.394	0.197	47.867	0.002
Rotation Speed	2	0.279	0.139	33.829	0.003
Residual	4	0.0165	0.004		
Total	8	0.690	0.086		
Tensile strength (MPa)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Mannitol: Cellulose Ratio	2	0.159	0.0793	10.559	0.025
Rotation Speed	2	0.00836	0.00418	0.557	0.612
Residual	4	0.0300	0.00751		
Total	8	0.197	0.0246		
Water absorption ratio (%)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Mannitol: Cellulose Ratio	2	1747.36	873.683	475.28	<0.001
Rotation Speed	2	77.918	38.959	21.19	0.007
Residual	4	7.353	1.838		
Total	8	1832.63	229.08		
Disintegration time (sec)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Mannitol: Cellulose Ratio	2	323.556	161.778	9.100	0.032
Rotation Speed	2	267.556	133.778	7.525	0.044
Residual	4	71.111	17.778		
Total	8	662.222	82.778		

DF is degree of freedom, SS is sum of square, MS is mean sum of square and F is Fischer's ratio.

Granular friability index

Granule strength and granular friability are critical factors because they can affect product quality. The directly compressible excipient is subjected to stress during processing (i.e. mixing and transportation), and friable agglomerates may not produce acceptable tablets. The granular friability index can be used as a quality control tool. After 60 min, the granular friability index and friability rate constant for batch S5 were 0.871 and 0.0021 min^{-1} (Figure 6). A value for the granular friability index close to one and the friability rate constant close to zero indicates that agglomerates are mechanically strong and have low friability against the external abrasion.

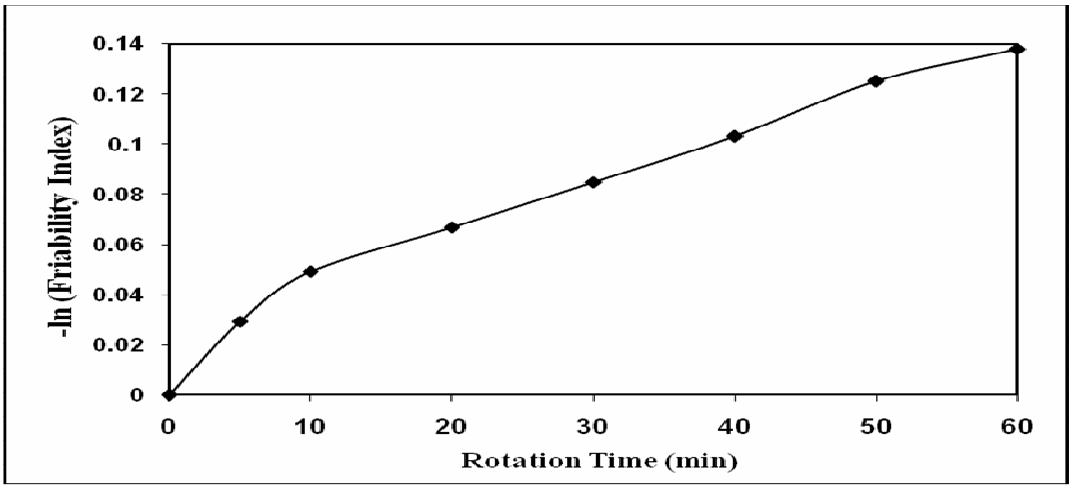

Fig. 6 : Granular friability index of batch S5

Heckel equation

Data obtained over the range of compression pressure 1 to 5 ton were analyzed by applying Heckel equation. The yield pressure (Py) was calculated from the reciprocal of the slope k of the regression line (Figure 7). Heckel reported that the linear portion of the plot represents the densification process by particle deformation after interparticle bonding and that soft, ductile powders have lower yield pressure. The agglomerates, which had the lower value, undergo plastic deformation as a result of the rebonding of smaller primary crystals than those of the original powder[26].

Mannitol prominently deforms by the fragmentation and cellulose is considered to be slightly elastic in nature. The Py value reflects the compression characteristics of the material; the lesser the value of Py, the greater is tendency towards plastic deformation. From the data shown in Table 5, it can be concluded that batch S5 exhibited plastic deformation compared with physical mixture of mannitol and cellulose (60:40)[26].

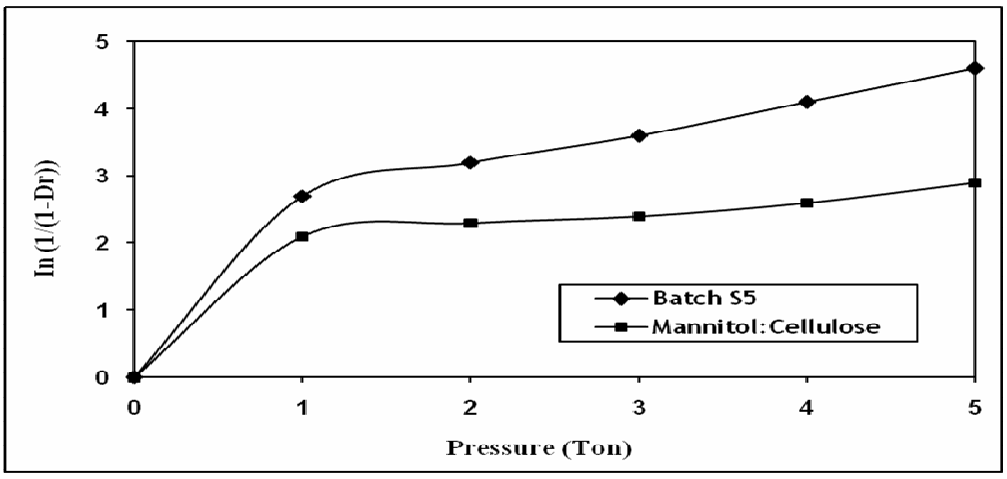

Fig. 7 : Heckel plot for batch S5 and Physical mixture

Table 5 : Properties of batch S5 and physical mixture of mannitol and cellulose

Ingredients	Parameter in Kawakita's Equation		Parameter in Kuno's Equation	Parameter in Equation Heckel Equation		
	a	b	K	A	k	Py
Physical mixture	0.466	0.079	0.032	0.900	0.460	2.173
Batch S10	0.303	0.117	0.021	1.061	0.788	1.269

Kawakita's and Kuno's Analysis

The packability 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" represents the packing velocity. The constant "a" for the batch S5 was smaller than for the physical mixture of mannitol and cellulose powder. The results indicate that the agglomerates of batch S5 show good packing even without tapping. The larger value of b for the batch S5 proved that the packing velocity of the batch S5 was faster than that of the physical mixture (Figure 8). The smaller value of "k" in the Kuno's equation supports the above findings (Table 5). The slow packing velocity corresponds with proportion of the consolidation of the powder bed per tap. The agglomerates of batch S5 showed improved compression property compared to physical mixture of mannitol and cellulose powder due to improved packability.

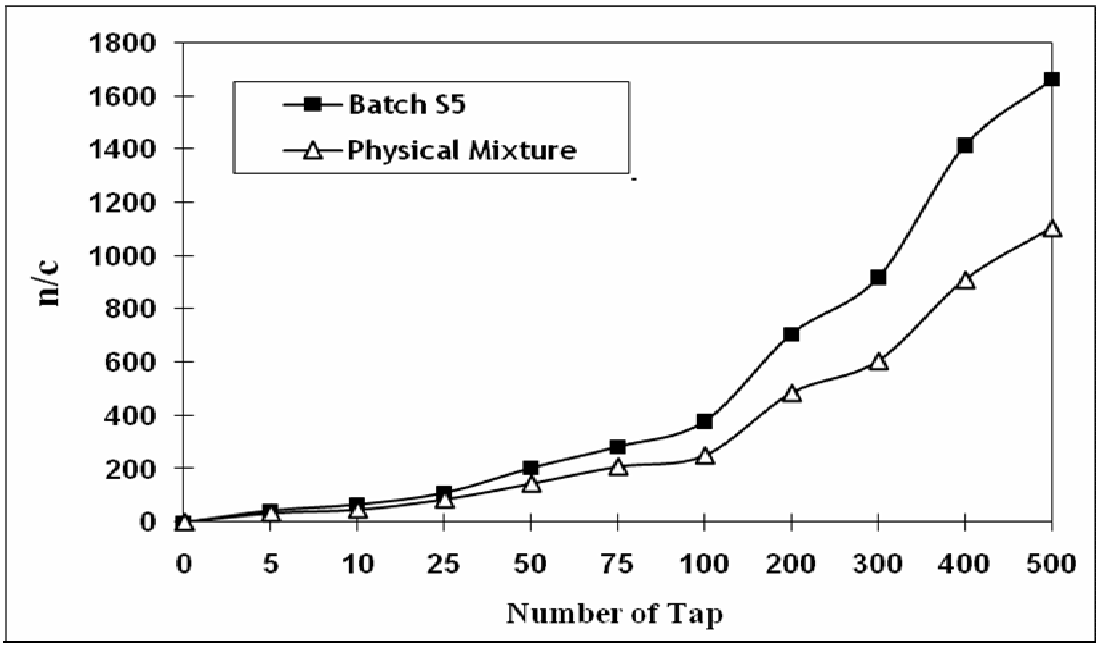

Fig. 8 : Kawakita's plot for batch S5 and physical mixture

Effect of lubricant

The Addition of magnesium stearate decreases the tensile strength of tablets. It is well known that prolong mixing of magnesium stearate produces the film around the agglomerates and prevents the binding of agglomerates. This effect is more pronounced in case of plastically deforming material than the material undergoing brittle fracture. In the light of these arguments and from the data shown in the Table 6, one can conclude that prolonged mixing of magnesium stearate decreases the tensile strength of the tablets. Lubricant sensitivity ratio is a quantitative measure to express the sensitivity of material to mixing with a lubricant. Higher the lubricant sensitivity ratio indicates more lubricant susceptibility. Mixing time exhibits higher effect on tensile strength as compared to compression time. Hence, it may be concluded that the agglomerates of batch S5 are less sensitive to lubricant.

Table 6 : Effect of magnesium stearate on agglomerates of batch S5

	L1	L2	L3	L4	L5
Agglomerates of Batch S5 (%)	100	99	99	99	99
Magnesium Stearate	--	1	1	1	1
Mixing time (min)	--	1	1	30	30
Compression time (sec)	1	1	30	1	30
Crushing Strength (kg)	7.2	6	7.1	5.8	6
Tensile Strength (MPa)	1.78	1.64	1.75	1.53	1.61
Lubricant Sensitivity ratio	-	0.16	0.013	0.19	0.16

Dilution potential study

Tablets were prepared using nimesulide (10-50%) as a model drug. The authors arbitrarily decided to select a batch that showed friability value < 1 % and tensile strength > 0.85 MPa. From the results shown in Table 7, it is quite evident that 30% nimesulide produce acceptable tablets. As the percentage of nimesulide was increased, the tensile strength decreased (Figure 9). This result might be caused by the poor compressibility and elastic recovery of nimesulide[27], which also affects the percent friability and disintegration time. Untreated mannitol and cellulose physical mixture did not yield satisfactory tablets even with 30 % nimesulide. This results shows that agglomerates of batch S5 exhibited higher compressibility and better binding property than the physical mixture.

Table 7 : Composition and results for dilution potential study

Ingredient	Batch code					
	D1	D2	D3	D4	D5	D6
Agglomerates of Batch S5	252	222	192	162	132	-
Physical Mixture (S5)	-	-	-	-	-	192
Nimesulide	30	60	90	120	150	90
Crospovidone	6	6	6	6	6	6
Sodium saccharin	3	3	3	3	3	3
Total Weight (mg)	300±12	300±14	300±09	300±15	300±10	300±12
Parameters						
Tensile Strength (MPa)	1.198	1.123	0.991	0.654	0.308	0.432
Friability (%)	0.11	0.69	0.83	2.68±	6.08	5.53
Disintegration Time (min)	4.5	5.3	6	4.2	5	4

All the batches containing 6 mg talc and 3 mg magnesium stearate

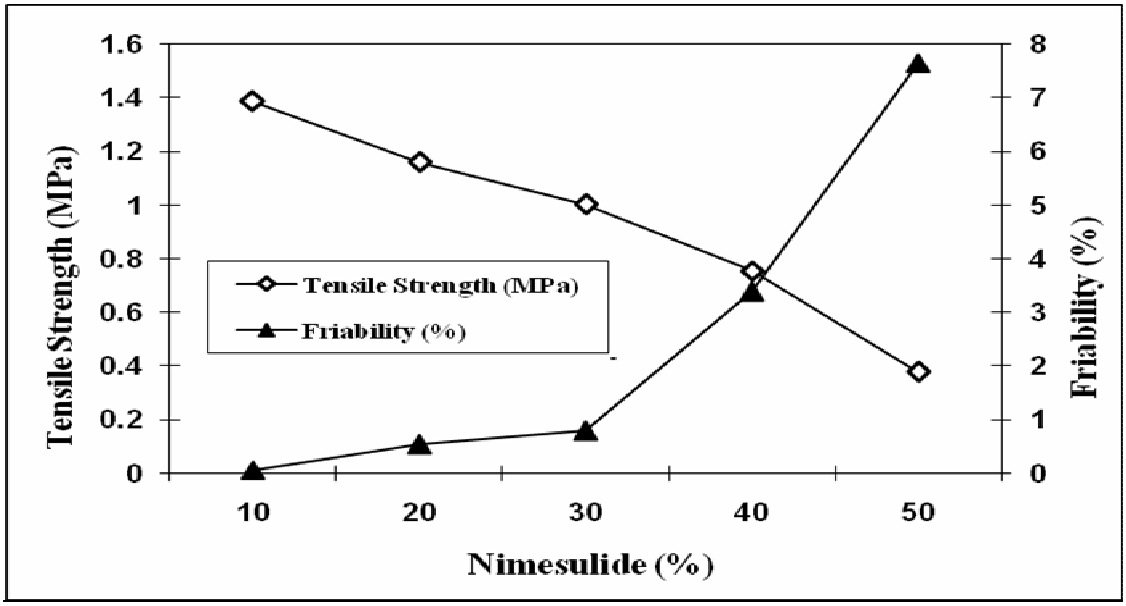

Fig. 9 : Effect of % nimesulide on tensile strength and friability

Moisture uptake

The agglomerates of batch S5 absorbed 14 % w/w of moisture when stored at 75 % relative humidity and 45˚C for 24 hr. This result may be due to the adsorptive nature of the cellulose[28]. The results revealed that batch S5 was reasonably moisture sensitive so, should be stored in tightly closed container.

Evaluation of tablets

From the results shown in Table 8, it can be concluded that the agglomerates of batch S5 exhibited satisfactory tableting characteristic with all the selected model drugs. The model drug formulations exhibited weight variation < 5%, friability < 1%, and disintegration time < 25 sec. An *in vitro* drug release study

showed that more than 40 % nimesulide and metformin HCl were released in 10 min from the respective tablets prepared using agglomerates of batch S5.

Short-term dissolution stability

Tablets containing nimesulide and metformin HCl were subjected to a short-term stability study (3 month, 45˚C/75 % RH). The drug release profile of tablets was compared with the marketed formulations (NIMULID-MD, Panacea biotech and FORMINAL, Alembic Pharmaceutical). The f_1 value was < 5 and f_2 value > 70 for the drug release profile of both the tablet formulations before and after the stability study[29] (Figure 10 & 11).

Table 8. Composition of the tablets using model drugs

Ingredients	**Nimesulide**	**Metformin HCl**	**Aceclofenac**
Drug (%)	30	50	50
Agglomerates of Batch S5	64	44	44
Crospovidone	2	2	2
Sodium saccharin	1	1	1
Parameters			
Average Weight (mg)	300 ± 10	1000 ± 42	500 ± 20
Tensile Strength (Mpa)	0.978 ± 0.01	0.860 ± 0.04	0.985±0.01
Friability (%)	0.691 ± 0.07	0.743 ± 0.03	0.625±0.02
Disintegration Time (Sec)	14	17	24
Dissimilarity factor (f_1)	5.02	4.97	--
Similarity factor (f_2)	72.67	72.08	--
All the batches containing 2% talc and 1% Magnesium Stearate			

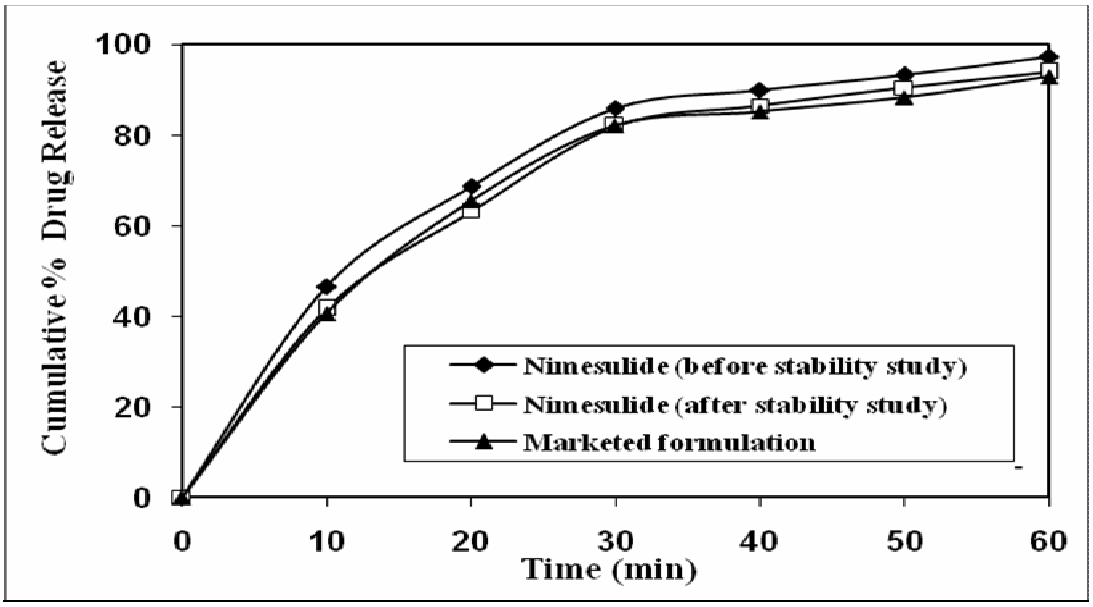

Fig. 10 : Comparative *in vitro* drug release profile of Nimesulide

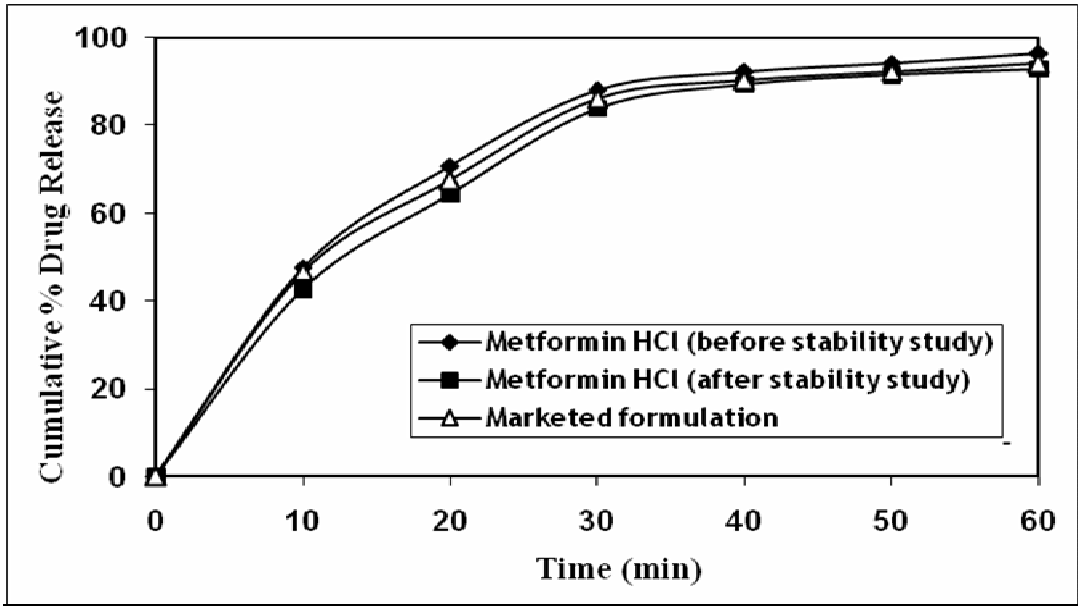

Fig. 11 : Comparative *in vitro* drug release profile Metformin HCl

CONCLUSION

The commercially available co-processed excipients are prepared by spray drying. The spray drying is burdensome and a relatively expensive procedure. The objective of present study was to develop a multifunctional directly compressible excipient using simple solvent free technique. Freeze-thawing technique has been found to be an alternative method that can be explored for production of directly compressible co-crystallized material. From the fines (%), carrs'index, friability, tensile strength, water absorption ratio, disintegration time, and composite index the batch S5 containing 60 and 40 parts of mannitol and cellulose was selected as optimized batch using 3^2 full factorial design. Heckel analysis showed that the agglomerates of batch S5 undergo plastic deformation compared to the physical mixture. The agglomerates were sensitive to high humidity. Hence, it is recommended that the agglomerates should be stored in tightly closed container for getting sufficient protection against moisture. Batch S5 agglomerates exhibited satisfactory dilution potential with Nimesulide as poorly compressible drug. Agglomerates exhibited satisfactory tablet properties with nimesulide, metformin HCl and aceclofenac. In summary, the co-crystallized agglomerates containing mannitol and cellulose can be used as a potential multifunctional directly compressible excipient. As per the results of this study it clearly indicated that the physical modification of mannitol and cellulose resulted in considerable improvement in its functionality as directly compressible material. The flowability and compactibility of the prepared agglomerates are prominent then the physical mixture.

REFERENCES

1. Jivraj M, Martin LG, Thomson CM. An Overview of the Different Excipients Useful for the Direct Compression of Tablets. PSTT 2000;3:58-63.
2. Armstrong NA, Palfrey LP. The Effect of Machine Speed on the Consolidation of Four Directly Compressible Tablet Diluents. J Pharm Pharmcol 1989;41:149-151.
3. Moreton RC. Tablet Excipients to the Year 2001: A Look into the Crystal Ball. Drug Develop Ind Pharm 1996;22:11-23.
4. Reimerdes D. The Near Future of Tablet Excipients. Manuf Chem 1993;64:14-15.
5. Casahoursat L, Lemogen G, Larrouture D. The Use of Stress Relaxation Trials to Characterize Tablet Capping. Drug Deve Ind Pharm 1988;14:2179-2199.
6. Kothari SH, Kumar V, Banker GS. Comparative Evaluations of Powder and Mechanical Properties of Low Crystallinity Celluloses, Microcrystalline Celluloses, and Powdered Celuloses. Int J Pharm 2002;232:69-80.
7. Daoust RG, Lynch MJ. Mannitol in Chewable Tablets. Drug Cosmet Ind 1963;93:26-28, 128-129.
8. Paradkar AR, Pawal AP, Mahadik KR, Kadam SS. Spherical Crystallization: A Novel Particle Design Technique. Indian Drugs 1994;31:229-233.
9. Nokhodchi A, Maghsoodi M, Hassanzadeh D, Barzegar-Jalali M. Preparation of Agglomerated Crystals for Improving Flowability and Compactability of Poorly Flowable and Compactible Drugs and Excipients. Powder Technol 2007; 175:73-81.
10. Patel SS, Patel PM, Patel NM. Evaluation of Direct Compression Characteristics of Co-processed Lactose Using Nimesulide. The Indian Pharmacist 2008;12:73-80.
11. Carr RL. Evaluating Flow Properties of Solids. Chem Eng 1965;72:63-168.
12. Gohel MC, Jogani PD. An Investigation of the Direct Compression Characteristics of Co-processed Lactose Microcrystalline Cellulose Using Statistical Design. Pharm Technol 1999;23:54-62.
13. Friability in USP XXIV-NF19, United State Pharmacopoeial Convention Inc. New York: Rockville; 2000;2148.
14. Disintegration Time in USP XXIV-NF19, United State Pharmacopoeial Convention Inc. New York: Rockville; 2000;1941.
15. Taylor MK, Ginsburg J, Hickey AJ, Gheyas F. Composite method to quantify powder flow as a screening method in early tablet or capsule formulation development. AAPS PharmSciTech 2000:Article 18.
16. Parrot EL. Milling in Theory and Practice of Industrial Pharmacy.

Lachman L, Liberman, HA, Kanig JL. editors. 3rd ed. New York: Lea and Febuger; 1986. p. 21-46.
17. Baykara T, Acarturk F. The Effect of Binding Agent on the Friability and Compressibility of Granules. Drug Dev Ind Pharm 1989;15:1341-1351.
18. Kawakita K, Ludde KH. Some Consideration on Powder Compression Equations. Pow Tech 1970;4:61-68.
19. Bolhuis GK, Zuurman K. Tableting Properties of Experimental and Commercially Available Lactose Granulations for Direct Compression. Drug Dev Ind Pharm 1995;21:2057-2071.
20. Heckel RW. Density-pressure Relationship in Powder Compaction. Trans Metall Soc AIME1961; 221:671-675.
21. Heckel RW. An Analysis of Powder Compaction Phenomena. Trans Metall Soc AIME 1961;221:1001-1008.
22. Bolhuis GK, Zuurman K. Tableting Properties of Experimental and Commercially Available Lactose Granulations for Direct Compression. Drug Dev Ind Pharm 1995;21:2057-2071.
23. Gohel MC, Jogani PD, Bariya SH. Development of Agglomerated Directly Compressible Diluent Consisting of Brittle and Ductile Materials. Pharm Dev Tech 2003;8: 143-151.
24. Metformin Hydrochloride Tablet, in Indian Pharmacopoeia Volume I, New Delhi: The Controller of Publication; 1996. p. 470.
25. Fiese EF, Hagen TA. Preformulation in Theory and Practice of Industrial Pharmacy. Lachman L, Liberman HA, Kanig JL. 3rd Ed. New York: Lea and Febuger; 1986.171-194.
26. Franziska F, Jiirgen R, Peter K. Coprocessing of Powdered Cellulose and Magnesium Carbonate; Direct Tableting Versus Tableting After Roll Compaction/Dry Granulation. Pharm Dev Tech 2005;10:353-362.
27. Lennartz P, Mielck JB. Minitableting: Improving the Compactibility of Paracetamol Powder Mixtures. Int J Pharm 1998;173:75-85.
28. Aulton ME. Cellulose Powdered, in Handbook of Pharmaceutical Excipients, Rowe RC, Weller PJ. Eds., UK: The Pharmaceutical Press; 2003. p.112-114.
29. Moore JW, Flanner HH. Mathematical Comparison of Dissolution Profiles. Pharm Tech 1996;20:64-74.