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PREPARATION AND EVALUATION OF MATERIAL PROPERTIES OF CO-PROCESSED DILUENT CONTAINING MODIFIED STARCH AND DICALCIUM PHOSPHATE

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ABSTRACT

The objective of present study was to develop a co-processed diluent consisting of physically modified starch and dicalcium phosphate and to assess its suitability in direct compression. Native starch was exposed to nitric acid under controlled conditions. Dicalcium phosphate was incorporated in the neutralized aqueous starch dispersion to prepare co-processed excipient. The modification did not cause any detectable change in the shape and size although rupture was observed in few starch grains. The co-processed diluent was evaluated for particle size analysis, flowability and compressibility. Acetaminophen and *glycyrrhiza glabra* powder were chosen as poorly compressible model drugs. Nitric acid treatment resulted in formation of starch with high crystallinity. The modified starch and co-processed excipient showed acceptable angle of repose, Carr's index, Hausner's ratio and tapped density. The tablets showed acceptable crushing strength, disintegration and friability. Co-processed diluents exhibited improved flow and compressibility. Starch contributed to economy and disintegration while dicalcium phosphate contributed fragmentation propensity and insulation towards moisture.

INTRODUCTION: Active pharmaceutical ingredients (API) are converted into a dosage form for variety of reasons. One of the attributes of an ideal dosage form is patient convenience. Tablet is the most preferred dosage form for oral delivery of API. Tablets are prepared in industry by direct compression, wet granulation and roller compaction. The most preferred method of manufacturing tablet is by direct compression due to simplified validation and ease of manufacturing [1].

In the recent years, drug formulation scientists have recognized that single-component excipients do not always give desirable results with most of the active pharmaceutical ingredients. Therefore, the combination of two excipients is commonly used. Combination excipients fall into two broad categories: physical mixtures and co-processed excipients. Physical mixtures are simple admixtures of two or more excipients typically produced by short duration processing at low shear. The problem of demixing of excipients can be seen due to the size and density differences [2].

Co-processed excipient is defined as a unique blend of two or more established excipients. Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components. Co-processing is interesting because the products are treated in a special way without altering the chemical structure [2, 3]. The main advantages of co-processing are improved flowability and compressibility.

Most active pharmaceutical ingredients exhibit poor flow, cohesive properties and poor lubrication. Therefore, they must be blended with other directly compressible ingredients. The cost of commercially available co-processed excipients is high mainly due to high cost of excipients, which are used to make it or high cost of processing. The cost of co-processed excipients is high if it is manufactured employing a patented excipient/process. One of the aims of the present investigation was to cut down the cost of co-processed excipient by employing an economical excipient (e.g. starch) in a relatively large proportion. Dicalcium phosphate (DCP) was selected as a second excipient considering its high fragmentation propensity, non- hygroscopicity and acceptability by FDA.

The second aim of the present study was to adopt a simplified manufacturing procedure for the preparation of co-processed excipient containing starch and DCP. The find aim was to assess the suitability of direct compression grade of the diluent employing acetaminophen and *glycyrrhiza glabra*, poorly compressible active ingredients.

MATERIALS AND METHODS:

Materials: Acetaminophen U.S.P. was received as a gift sample from Green Pharma, Ahmedabad (India). *Glycyrrhiza glabra* powder was purchased from a local Ayurvedic Pharmacy, Ahmedabad (India). Wheat starch I.P. and di-calcium phosphate were purchased from Anil Starch, Ahmedabad (India) and Ranbaxy Fine Chemicals, New Delhi (India) respectively. Nitric acid was purchased from Finar Chemicals Pvt. Ltd, Ahmedabad (India). Aerosil 200 and Crosspovidone were received as gift samples from Zydus Cadila, Ahmedabad (India). Talc and magnesium stearate were purchased from Loba Chemie Pvt. Ltd, Mumbai (India) and Central Drug House, New Delhi (India) respectively. Distilled water was used throughout the study. All other chemicals were of reagent grade.

Methods:

Preparation of acid treated starch: One thousand gm of wheat starch was blended with 100 ml of 0.8N nitric acid. The mixture was stored at ambient condition (29^{o}C) for 24 h with occasional stirring.

The liquid was separated from solid and the wet cake was washed with distilled water to eliminate the traces of acid. The process of washing was continued till the pH of washing was equal to that of distilled water. The acid treated starch was dried at 75^{o}C for 16 h and stored in a sealed container after passing it through a # 30 sieve [4, 5].

Preparation of Co-processed excipient: The result of preliminary study revealed that the yield of dry acid treated starch was 92%. Di-calcium phosphate (25% of the expected yield of the dry acid treated starch), was thoroughly mixed with the washed wet cake prepared earlier. The wet mass was dried at a temperature less than 75^{o}C till the moisture content of powder was dropped to approximately 2% w/w. The excipient blend was passed through a #30 sieve and the yield of dried granules was recorded. The granules were stored in a sealed polyethylene bag till further use.

Preparation of drug (acetaminophen or *glycyrrhiza glabra*) excipient blend: The drug sample was sieved through a # 60 sieve. The drug powder was mixed with Aerosil 200 (0.5% w/w) to improve the flow of the drug particles. The drug-Aerosil blend was lubricated with talc (1% w/w) and 0.5% w/w magnesium stearate.

Preparation of drug (acetaminophen or *glycyrrhiza glabra*) tablet: Co-processed excipient containing 75% w/w of treated starch and 25% w/w DCP was blended with drug-excipient blend (acetaminophen/*glycyrrhiza glabra*, Aerosil, talc and magnesium stearate) in a ratio of 70 to 30. Four percentage of Crosspovidone was used as an extra granular disintegrant. The blend ready for compression was stored in a sealed polyethylene bags. The mixture was compressed on a single punch tablet machine (Cadmach Machinary Co., Ahmedabad, Type No-CMS, Serial No- H 110/75).

Material properties:

Optical microscopy: Microscopic study of native starch, acid-treated starch and co-processed excipient was carried out employing an optical microscope (Labomed Monocular microscopy model CXL plus). Lewandowicz and Smietana method (2004) was adopted with little modification (heated at 60^{o}C for 15 min) for microscopic study [6].

Average particle size: Microscopic examination of a sample of a powder was carried out. The number of particles lying within various size ranges was recorded. Edmundson has derived a general equation for determining the average particle size which is as follow:

$$d_{mean} = (\Sigma nd^{p+f} / \Sigma nd^{f})^{1/p}$$

Where n is the number of particles in a size range, d is one of the equivalent diameters, p is an index related to the size of an individual particle and f is frequency index. The values of p and f were considered to be one assuming that the particle length was measured in the microscopic study [7].

Particle size distribution: Rotap sieve shaker was used to determine particle size distribution (International Combustion Ltd, London and Derby, M/C No- 666, S/N- 8095/G058). Particle size distribution of materials is depicted in **Table 1, Fig. 1 and 2**.

Angle of repose: The static angle of repose was determined by fixed funnel method. The funnel was mounted over a base free of vibration. The funnel height was adjusted in such a fashion that the tip of funnel was 3cm above the pile tip. Sample was allowed to fall freely on stationary base. The angle of repose was determined by measuring height of the cone of sample. Grading of the flow was done as per USP. The following equation was used to compute angle of repose (α) [8];

$$\tan \alpha = \text{height of powder pile} / \text{radius of base}$$

Measurement of densities: Tapped density was measured by using a digital tester (USP II, Electrolab, Model no- ETD- 1020). The loose bulk density was determined for each sample by pouring 30 gm of the sample at an angle of 45^0 through a glass funnel into a 50 ml glass measuring cylinder with 28 mm diameter [9]. Compressibility index (I) and Hausner's ratio (H) were computed by the following equations [10]:

$$I = V_0 – V_f / V_o;$$
$$H = V_0 / V_f$$

V_o is volume before tapping, V_f is volume occupied by a sample of the powder after being subjected to a standardized tapping procedure.

Determination of water content: The moisture content was determined by drying 10 gm of each sample in a vaccum oven at 110±2°C for 2 h. The percentage loss in weight was recorded as moisture content [11].

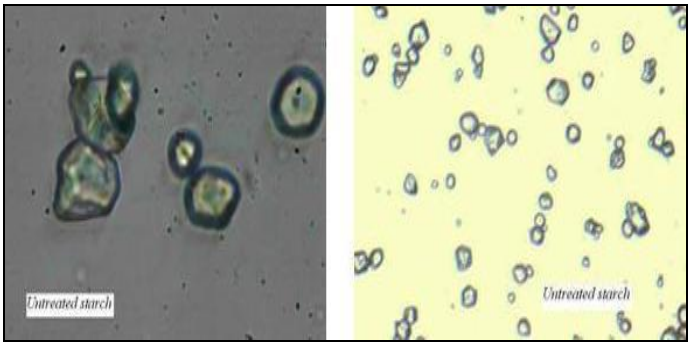
Determination of amylose content: 100mg of acid treated starch was heated for 10 min with 1ml of 95% v/v ethanol and 9ml of 1 N caustic soda in a boiling water bath to gelatinize the starch. The liquid was cooled to room temperature and then it was diluted to 100ml with distilled water. 5ml of the starch solution was transferred to a 100ml volumetric flask. One ml of acetic acid and 2ml of iodine solution were added, followed by dilution to 100 ml with distilled water. After 20 min, the material was shaken and the absorbance was measured at 620nm [9] employing a spectro-photometer (1700 Pharmaspec, Shimadzu).

Percentage amylose = 3.06 × absorbance × 20

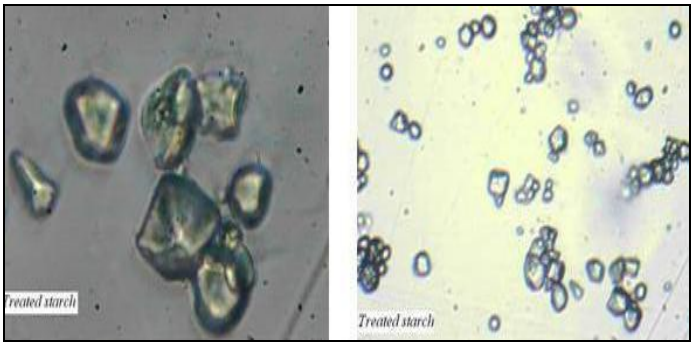
Thermal analysis: The analysis was done employing DSC-60 (TA-60 WS, Shimadzu Corporation, Kyoto, Japan) using sealed stainless steel pan. The sample and reference pan were heated from 298^0 K to 433^0 K at a scanning rate of 10°K/min. The samples were held for 2 minutes at 433°K, and cooled to 333°K at 10°K/min [12].

TABLE 1: RESULTS OF EVALUATED PARAMETERS FOR EXCIPIENTS

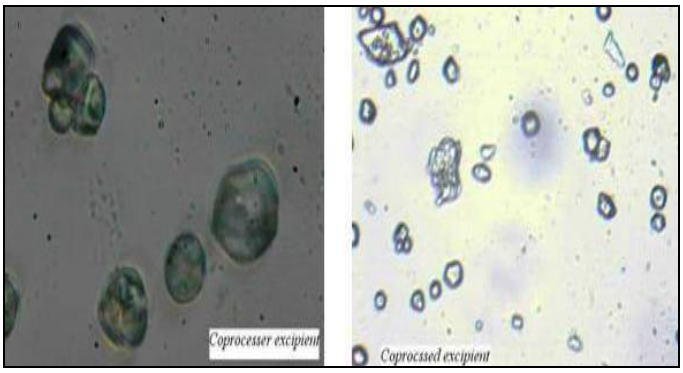
Evaluated parameter	Native starch	Dicalcium phosphate	Co-processed diluent (3:1)	Acid treated Starch
Angle of repose (^{0})	44	32	31	27
Moisture content (%)	11	-	1.35	1.87
Yield (%)	-	-	91.78	92.52
Color	White	White	White	Off-white
Bulk density (gm/cc)	0.458	0.75	0.54	0.63
Tap density (gm/cc)	0.611	0.94	0.63	0.74
Carr's index (%)	25	20	14	14.5
Hausner's ratio	1.38	1.25	1.12	1.16



(A) NATIVE STARCH



(B) ACID TREATED STARCH



(C) CO-PROCESSED DILUENT

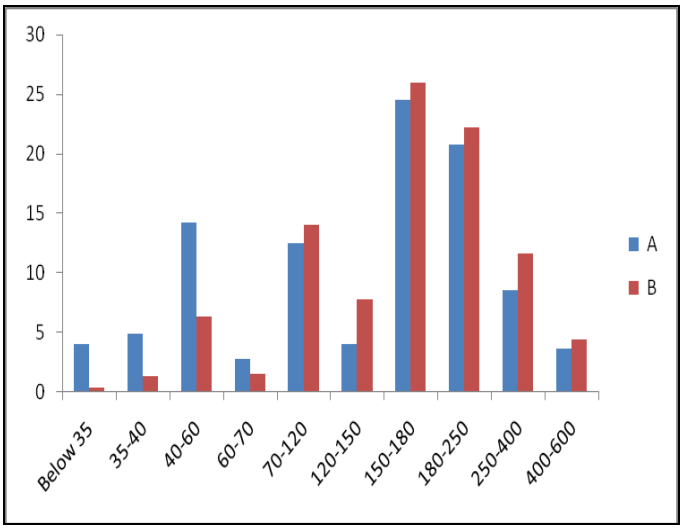


FIG. 2: (A) PARTICLE SIZE ANALYSIS OF ACID TREATED STARCH; (B) PARTICLE SIZE ANALYSIS OF CO-PROCESSED DILUENT

Tablet properties:

Uniformity of mass: Twenty tablets were individually weighted. Not more than two of the individual tablet deviate from the average mass by more than 7.5% deviation (uncoated, single dose, 300mg or more) [13].

Fineness of dispersion: Two tablets were dispersed in 100ml of water. The dispersion was passed through a screen with a nominal aperture of 710µm [14].

Disintegration: Disintegration test of all tablets was carried out in USP disintegrating tester (Electrolab, ED-2L). Disintegration of six tablets was measured at 37°C [14].

Crushing strength: Crushing strength of each tablet was determined using Dr. Schleuniger crushing strength tester (Pharmatron, tablet tester 8M).

Tablet friability: Friability of the tablets was determined in USP apparatus (Electrotab friabilator USP (XXIII), Model no-EF-2, Mumbai). The tablets were carefully dedusted prior to testing. Tablets corresponding to 6.5 gm weight were charged in the friabilator. The drum was rotated for 4 min. Loose dust was removed from the surface and the weight of tablet was recorded. A maximum mean weight loss from three samples of not more then 1% is considered acceptable [15].

RESULTS AND DISCUSSION: Native starch exhibit poor flow and poor compressibility. Hence, it is not widely used as a diluent in direct compression. Starch can be modified by adopting chemical or physical means. Starch acetate has been explored for preparation of tablets [16]. However, the use of derivatized starch has not percolated in the pharmaceutical industry, mainly due to regulatory clearance. Acid treatment preferentially attack amorphous region of starch (amylose), while the crystalline regions remain unaffected (amylopectin). Acid treatment of native starch, at temperatures lower than the gelatinization temperature, can increase the relative crystallinity of starch [17].

Material properties: Fig. 1 shows that native starch consisted of small spherical to ovoid granules. Acid treated starch exhibited spherical shape. However, few particles ruptured during the acid treatment. Co-processed excipients did not show fragments of starch. Co-processed excipient showed microscopy similar to the native starch. For the determination of particle size (diameter/length), the parameters p and f were considered as one, in the equation

mentioned in the experimental section. The arithmetic mean particle size was computed as 236µm. Sieving is basically a very simple and a popular particle-sizing technique. A useful guide to the choice of the number of sieve in a nest, and their respective aperture size, is that not more than 5% w/w of the test sample should be retained on the coarsest sieve and not more than 5% w/w should pass through the finest [18]. Particle size distribution of acid treated starch and co-processed excipients is shown in Figure 2. Maximum particles were found in between 150-250µm range in both the samples. The percentage of fines was less than 10% in acid treated starch and co-processed diluent.

The characterization of powder flow was done as per the recently introduced chapter on powder flow in USP [9]. The flow was graded as excellent, good, fair and passable for angle of repose 25-30^o, 31-35^o, 36-40^o and 41-45^o respectively. The angle of repose of native wheat starch, acid treated starch and co-processed excipient was 32^o, 27^o and 30^o respectively. Accordingly, native starch exhibited passable flow, i.e. the powder may hang up in hopper.

The reason for poor flow of native starch may be attributed to higher percentage of fines than the co-processed diluents and acid treated starch. The results shown in Table 1 reveal that the other samples exhibited good to excellent flow [8]. The data shown in **Table 2** displays that the drug-excipient blend exhibited good to fair flow, with angle of repose 35^{o}C for acetaminophen and 37^{o}C for *glycyrrhiza glabra.* The values of the bulk and tapped densities provide information on the flowability of powders and are used to calculate the Carr's index which is a measure of the flowability and compressibility of a powder. The lower the Carr's index of a material, the better the flowability [12]. The Hausner's ratio provides an indication of the degree of densification, which could result from vibration of the hopper [9]. Low Hausner ratio of co-processed excipients and acid treated starch indicate better compressibility than native starch (See Table 1). For characterization of flow, compressibility index (%) and Hausner ratio ranges were obtained from USP.

TABLE 2 RESULTS OF EVALUATED PARAMETERS OF MODEL DRUG-EXCIPIENTS BLEND

Evaluated parameter	Drugs with all additive*	
	Acetaminophen	*Glycyrrhiza glabra*
Angle of repose (^{0})	35	37
Color	White	Brownish
Bulk density (gm/cc)	0.559	0.49
Tap density (gm/cc)	0.681	0.63
Carr's index (%)	17.91	21.88
Hausner's ratio	1.21	1.28

*Aerosil, crosspovidone, magnesium stearate and talc all are present in previously described proportion.

The results shown in Table 1 reveal that native starch exhibited poor to passable flow (I = 21-25% and H = 1.35-1.45). Dicalcium phosphate exhibited fair flow. The other samples, shown in Table 1, exhibited good flow (I = 11-15% and H = 1.12-1.18). There are two primary requirements for directly compressible diluents, i.e. good flow and good compactability. The second attribute (i.e. good compactability) has been addressed later in the paper.

Moisture typically equilibrates to about 12 % or less in native starch powder [9]. In present work, the moisture content of acid treated starch was lower than 3%. The improved flow of acid treated starch may be attributed to lower moisture content. The amylose content in native starch and acid treated starch was 17% and 7% respectively. The amylose content of the co-processed excipient was 13%. Co processing of starch with DCP influenced the effectiveness of acid. One of the possible reasons could be partial solubilization of DCP in nitric acid. Differential scanning calorimetry measures heat flow as a function of sample temperature. It is used in both product research and quality control for characterizing material

properties, such as glass transition temperature, melting temperature, transition enthalpies, specific heat, polymorphism, purity, thermal and oxidative stability [19]. The samples of native starch and dicalcium phosphate showed endothermic peak at 85.03°C (**Fig. 4**) and 195.44°C (**Fig. 5**) respectively. Co-processed excipient showed peaks 88.95°C, 193.49°C, 257.83°C and 280.29°C (**Fig. 6**). On inspecting the DSC spectra, it can be concluded that the changes are physical. The peak at 280.29°C may be gelatinized product peak, present in the acid treated starch in small amount. A peak at 257.83°C may be due to water evaporation or poor conductivity of starch [11].

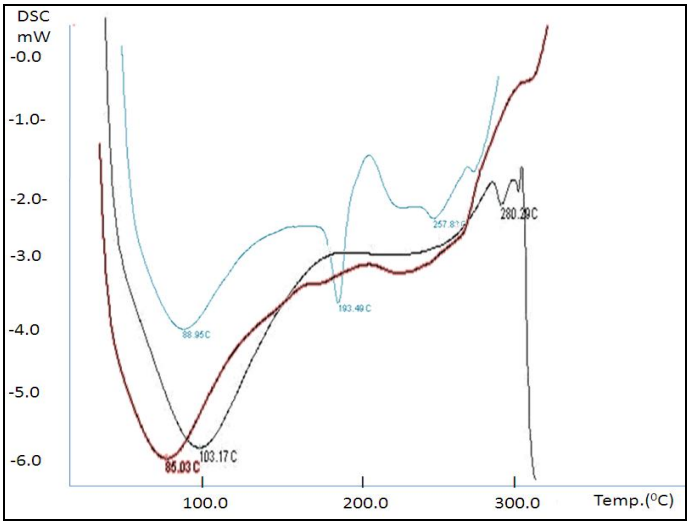


FIG.3: DSC SCAN; RED LINE SHOWS NATIVE STARCH, BLACK LINE SHOWS ACIDIFIED STARCH AND BLUE LINE SHOWS CO-PROCESSED DILUENTS

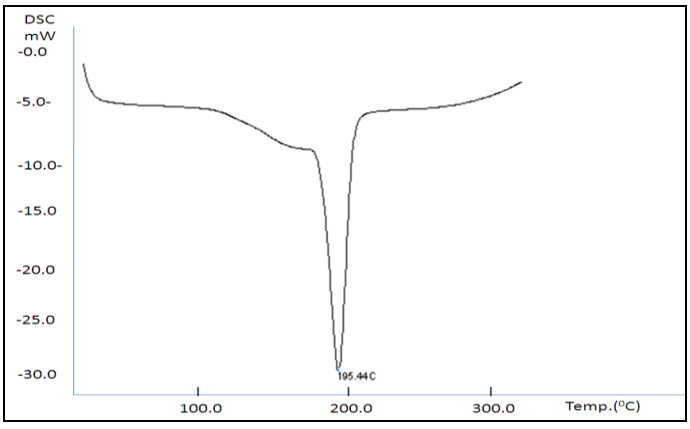


FIG.4: DSC SCAN OF DICALCIUM PHOSPHATE

Tablet properties: The use of direct compression is limited in industry due to flowability, content uniformity and tablet ability problems. Flowability and tablet ability are of concern in high dose tablet while content uniformity is of concern in low dose tablet. Generally small size drug particles are used in direct compression. Hence, poor flow and poor content uniformity may be seen. The problem of poor flow of drug can be addressed by mixing of 0.5% glidant with drug (first step of glidant addition) and remaining 0.5% glidant and other ingredients were mixed in drug-glidant mixture (second step of glidant addition).

Abe *et al.,* recommended two step additions of glidant [20]. The first step of glidant addition would result in formation of coat around drug particles. Acetaminophen tablets are made by using wet or dry granulation method due to the flowability and compressibility issues. In the present work, direct compression was used for preparing acetaminophen and *glycyrrhiza glabra* (a fibrous herbal drug) tablets. Acetaminophen and *glycyrrhiza glabra* exhibited good flowability when 0.5% glidant was blended separately before adding the other ingredients. Good flow is a pre-requisite for good mixing. The tablets showed little deviation in weight and quick disintegration. When the dispersions were passed through 710µm, no particles were retained on sieve.

The data of friability, crushing strength and disintegration time of drug free tablets (excipients only) are shown in **Table 3**. The tablets of acid treated starch exhibited shorter disintegration time, due to less damage (gelatinized) to starch granules. The gelatinized starch impedes the penetration of water into the tablet and thus prolongs tablet disintegration [17]. The tablets of co-processed excipients exhibited relatively higher disintegration time as compared to acid treated starch. All tablets disintegrated in less than 1 min.

TABLE 3: FRIABILITY, CRUSHING STRENGTH AND DISINTEGRATION TIME OF TABLET (WITHOUT API)

Evaluated parameter	Combination of native starch and DCP (3:1)	Di-calcium phosphate	Acid treated starch	Co-processed excipients (3:1)
Friability (%)	> 1	0.32	1.06	0.76
Crushing strength (kg)	< 1	11	2	5
Disintegration time (sec)	25	›10	38	40

Fast disintegration may be attributed to weakening of hydrogen bonds in the presence of excess moisture [21]. Acid hydrolysis attacks the amorphous regions resulting in a stronger packing under the application of compression force. Acid treatment resulted in marginal increase in the crushing strength of the tablets. It has been reported that the crystalline region would be forced closer together during compression which will result in an increase in tablet strength [11]. Co-processing is carried out at sub-particle level and hence it improves the binding of the tablet [22]. Table 3 reveals that crushing strength of co-processed and acid treated starch was 5 and 2kg respectively. High fragmentation propensity of DCP may be responsible for this observation. The crushing strength of acetaminophen and glycyrrhiza glabra tablets was found to be dependent on the amount of drugs (see **Table 4**).

TABLE 4: FRIABILITY, CRUSHING STRENGTH AND DISINTEGRATION TIME OF TABLET CONTAINING ACETAMINOPHEN AND GLYCYRRHIZA GLABRA

Evaluated parameter	Acetaminophen (%)			Glycyrrhiza glabra (%)		
	30%	40%	50%	30%	40%	50%
Friability (%)	0.52	0.87	1.67	0.64	0.65	0.83
Crushing strength (kg)	5.9	5.09	2.24	7.23	5.2	5.09
Disintegration time (sec)	40	30	20	44	38	30

Friability is inversely proportional to the crushing strength and it should be less than unity (i.e. 1). Friability of co-processed tablets (Table 3) was lower than that of acid treated starch. Friability of acetaminophen and glycyrrhiza glabra increased linearly as the proportion of drugs was increased. The results shown in Table 4 imply that upto 40% acetaminophen and 50% glycyrrhiza can be incorporated in the tablet.

CONCLUSION: Acid treated starch and co-processed diluent containing starch plus dicalcium phosphate exhibited improved flowability as measured by angle of repose, compressibility index and Hausner's ratio. The lower moisture content and lower percentage of fines could be the reasons for improved flow of co-processed diluent. Glycyrrhiza glabra tablets exhibited acceptable crushing strength and quick disintegration into primary particles. The salient points of the co-processed diluents are low moisture content, low cost, ease of availability of raw materials, quick disintegration of tablets and possibly regulatory acceptance. The process can be converted in one pot process if the pharmacist and chemical engineers work in concert. In future, moisture sensitivity and microbiological load will be addressed by us.

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