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Evaluation of Synthesized Cross-linked Tragacanth as a Potential Disintegrant

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Cross-linked tragacanth was prepared using epichlorhydrin. The effects of ratio of tragacanth to epichlorhydrin, temperature and time of reaction were studied. The cross-linked tragacanth was evaluated for swelling capacity, hydration capacity and moisture sorption capacity. Dispersible tablets of albendazole were prepared and evaluated. The cross-linked tragacanth exhibited superior wicking and swelling action and hence can be used as a superfunctional disintegrant. A simple test is proposed for measuring water uptake rate by the tablets. The results of the test showed good correlation with the disintegration time. The cross-linked tragacanth was found to be effective both in soluble lactose system and the insoluble dicalcium phosphate system.

ALBENDAZOLE is one of the most potent broad spectrum benzimidazole carbamate anthelmintics[1]. It is a very effective alternative to mebendazole or pyrantel pamoate. It is widely prescribed for children having age less than two years at a dose of 200 mg.

A greater importance is given to the disintegration and dissolution characteristics of tablets since bioavailability may be related with these factors. During the last two decades, pharmaceutical researchers have tried different adjuvants to improve product performance. Shangraw and co-workers reviewed the modern disintegrants and compared their relative morphological properties[2,3]. Few effective disintegrants such as sodium starch glycolate[4], cross-linked polyvinylpyrrolidone (CLP)[4], cross-linked sodium carboxymethyl cellulose[5] have been evaluated. In the present investigation, the method of preparation of cross-linked tragacanth was optimized and later it was tried as a disintegrant for the development of albendazole dispersible tablets.

EXPERIMENTAL

Materials

Albendazole and cross-linked polyvinyl pyrrolidone were obtained as gifts from Torrent Pharmaceuticals, Ahmedabad and GAF Corp., U.S.A., respectively. All other chemicals were of reagent grade and were used as received.

Cross-linking of Tragacanth

A chemical method was used for the preparation of cross-linked tragacanth. Dry tragacanth powder and epichlorhydrin in ratios ranging from 1:0.2 to 1:0.8 were allowed to react at temperatures ranging from 37° to 105°. The reaction time was varied in between 45 and 180 min.

Swelling Capacity[6]

One gm of the material was mixed each with water and linseed oil. The samples were centrifuged for 20 min at 2000 R.P.M.

% Swelling Capacity = (DS * 100) / Volume in oil

Table 1 : Evaluation of Distinegrants

Intrinsic Properties	CLT	CLP	CS
Swelling capacity (% v/v)	142.0	42.1	5.8
Absorption efficiency (% w/w)	40.3	47.3	7.9
Moisture sorption capacity (% w/w)	48.6	55.6	11.4
Setting volume (mL)	7.8	10.6	2.7
PSD (μ)			
0-25	19	23	80
26-50	21	39	20
51-75	35	20	00
76-100	11	03	00
101-125	09	05	00

CLT = Cross-Linked Tragacanth,
CLP = Cross-Linked Polyvinyl Pyrrolidone,
CS = Corn Starch, PSD = Particle Size Distribution

Conditions of cross-linking : Tragacanth : epichlorhydrin 1:0.4
Reaction Time 45 min, Temperature of Reaction 105°

Table 2 : Formulation of Albendazole Tablets

Batch Code	Weight in mg			
	CLT	SP	DCP	Lactose
A	60	7.5	0	123.5
B	36	15.0	0	140
C	36	7.5	140	7.5
D	48	7.5	70	65.5
E	48	11.0	0	132
F	36	11.0	70	74
G	44	10.0	46	91

Albendazole = 200 mg
SP = Starch, DCP = Dicalcium Phosphate

Where, DS is the difference in sediment volume. The % moisture sorption capacity was calculated by the reported method[7]. The absorption efficiency[8] was calculated in a similar way as dissolution efficiency. The area under the curve (AUC) was calculated from the plot of % moisture sorbed as a function of time.

Table 3 : Results of Evaluation of Tablets

Property	Batches						
	A	B	C	D	E	F	G
Hardness	5.02	5.08	5.04	5.02	4.96	4.92	4.88
Friability	2.23	1.62	2.12	1.71	1.29	1.35	1.43
Disintegration Time (Sec.)	98	201	40	141	89	165	222
Wetting Time (Sec.)	347	480	227	382	279	415	534

Absorption efficiency = (AUC * 100) / Total area

The tests were also carried out on reference disintegrants such as cross-linked polyvinylpyrrolidone (CLP) and corn starch (CS). Particle size distribution, settling volume[9], pH of aqueous dispersion and moisture content were also determined for the optimized batch of cross-linked tragacanth. The result of the tests and the optimum conditions for corsslinking of tragacanth are shown in Table 1.

Preparation of Albendazole Tablets

Tablets of albendazole of 400 mg average weight were prepared by wet granulation method. The drug, crosslinked tragacanth (36 to 60 mg), starch (7.5 to 15 mg, added in paste form), dicalcium phosphate (0 to 140 mg), lactose (7 to 140 mg) and auxiliary adjuvants were processed to yield tablets. The same volume of binder solution was used in all the batches. Talc (1%), magnesium stearate (0.75%), sodium lauryl sulphate (0.5%) and sodium saccharin (0.01%) were used as auxiliary adjuvants in all the batches. The formulations of different batches (A to G) are depicted in Table 2.

Evaluation of Tablets

The hardness and friability of the tablets were measured using a Monsanto hardness tester and a Roche friabilator respectively. The drug content was determined by spectrophotometric method. The absorbance measurements were made at 290 nm from methanolic HCl solutions. The disintegration test was carried out as per USP XXI at room temperature in 900 mL distilled water using an Electrolab digital disintegration tester (Model: ED2). The average values of three observations are shown in Table 3.

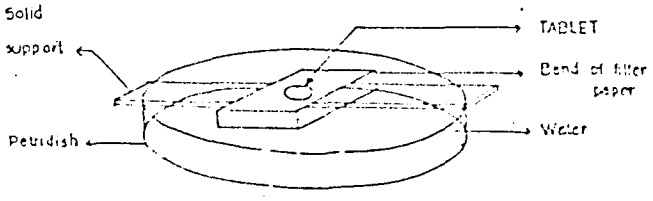


Fig.1 Set-up of Wettability Study

Wettability study

A simple experiment was designed to estimate the water uptake of the formulated tablets. The experimental set-up is shown in Fig. 1. A glass petridish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time. The average of three observations are shown in Table 3.

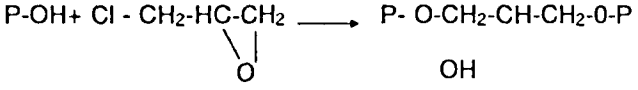
Albendazole tablets of batch C were subjected to the dissolution study (USP XXI, 900 mL, 0.1 N HCl, pH 1.2) since they exhibited superior wetting and disintegrating properties. The rate of rotation of paddle was maintained at 100 rpm. The drug content was determined in the aliquots withdrawn at predetermined time.

Toxicity study[10] of CLT as well as stability and microbial study[11] for the prepared tablets were carried out.

RESULTS AND DISCUSSION

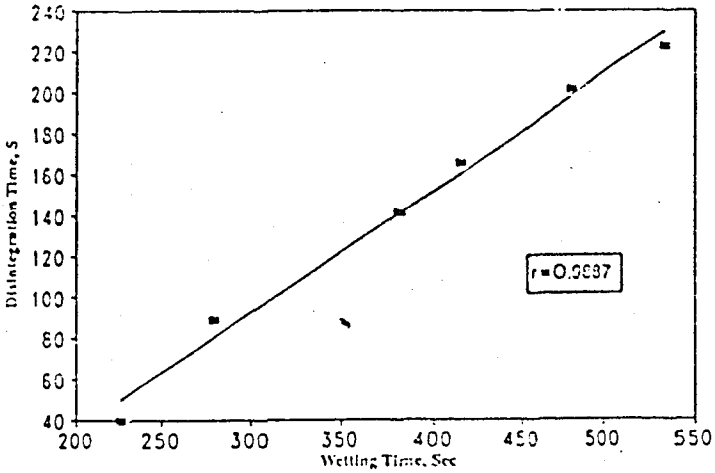
The minimum amount of epichlorhydrin necessary to achieve cross- linking was found to be 0.4 part for every part of tragacanth. The results also revealed that at 37°, crosslinking of tragacanth was not achieved at all the ratios tried in the present study. As the boiling point of epichlorhydrin is 116°, the cross-linking reaction was carried out in the range of 60° to 105°. The temperature of cross- linking reaction exhibited significant effect on the reaction rate. Based on the results of intrisinc properties, optimum conditions for cross-linking of tragacanth were found to be: a) 1:0.4 ratio of tragacanth:epichlorhydrin, b) temperature of reaction as 105° and c) time of reaction as 45 min. The yield at the specified reaction conditions was found to be 73% w/w. The optimized batch was used for further investigations. The results of intrinsic properties of the batch are shown in Table 1.

It was found that the treated material exhibited quicker hydration and higher swelling. The hydroxyl groups on the tragacanth may have reacted with epichlorhydrin as shown below :



Where, 'P' represents polymer. As depicted in Table 1, the prepared sample of CLT showed higher swelling capacity was compared to CS and CLP. The moisture sorption capacity for the sample of

FIG.2 EFFECT OF WETTING TIME ON DISINTEGRATION



CLT was found to be higher (48.6) than that of CS (11.4) but almost similar to that of CLP (55.6). The DSC showed an additional peak in the treated sample. Based on the results of the intrinsic properties and DSC it may be concluded that structurally modified tragacanth is formed.

Cross-linked tragacanth showed relatively wide particle size distribution and less settling volume as compared to CLP. The pH of the aqueous dispersion of CLT was found to be 6.8. Cross- linked tragacanth was found to be harmless at a dose of one g per kg body weight of mice when administered orally.

The optimized batch of CLT was used for the preparation of albendazole dispersible tablets. The formulations and the results of evaluations are depicted in Tables 2 and 3 respectively.

The data demonstrate that the tablets of batch C showed least disintegration time (40 sec) and least wetting time (227 sec). A good correlation (Fig. 2, r = 0.9887) has been observed between wetting time and disintegration time. The tablets containing CLT swelled during disintegration. Hence, it may be concluded that the mechanisms of action are wicking and swelling. The solubility of major component in

Table 4 : Corporative Performance of Disintegrants

Material	CLT		CLP		CS		
Proportion(%)	9	5	9	5	12	9	5
Disintegration Time (Sec.)	40	157	20	28	95	232	673

a tablet formulation affects both the rate and mechanism of tablet disintegration. Dicalcium phosphate (DCP, water insoluble in nature) promoted water uptake by CLT particles, whereas, lactose (water soluble diluent) competes for water. It is probable that lactose may have formed a diffusion barrier layer of saturated lactose solution around the tablet. This diffusion layer may impede the availability of water to the CLT particles, slowing the rate of water uptake by the tablet. It has been previously reported that water penetrates in DCP tablets at a faster rate even in lubricated tablet containing no disintegrant.[12,13] The probable reason for this behaviour may be the absence of diffusion barrier layer since DCP is insoluble in water. The desired disintegration time for lactose containing tablets can be obtained by optimizing the proportion of binder and disintegrating agent. It has been reported that a disintegrating agent is needed to overcome the negative effect of magnesium stearate to promote water penetration into tablets containing lactose monohydrate[12,14].

The tablets containing 9% CLT disintegrated in 40 sec (Table 4). The tablets in which CLT was omitted remained intact for more than four hours, probably due to hydrophobic nature of the drug. The tablets containing 9% tragacanth gum exhibited disintegrating time of 58 min., probably because of binding action offered by tragacanth gum.

The CLT was found to be more effective at 9% level that at 5% level, whereas CLP was found to be equally effective at 5 and 9% levels. Corn starch, when used at 12% level did not show comparable results.

The difference in the performance between CLP and CLT can be explained on the basis of bulk density and particle size distribution. The bulk density of CLP was found to be very low as compared to CLT. Bolhuis and co-workers[15] also reported that in addition to chemical differences, particle size of different sodium starch glycolate played critical role in tablet disintegration. The tablets 5% containing CLP showed superior characteristics probably because of higher surface area and uniform distribution of the disintegrating agent in the matrix of the tablets. More than 5% of CLT is required because of its higher bulk density and larger particles..

The dissolution study of tablets of batch C showed that the drug was completely released within 30 min. Microbial study was carried out at 37°/75% RH for 1 month for the tablets of batch C. Total microbial count and mold/yeast counts were found to be within limits prescribed for oral preparations[11]. The product was found to be chemically stable when tested for short term stability study (room temperature (R.T.), R.T./75% RH and 45° for 30 days). In conclusion, the results of the present investigation indicate that cross-linked tragacanth shows potential of a good disintegrating agent and may be used for import substitution.

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