

Evaluation of Synthesized Cross Linked Polyvinyl Alcohol as Potential Disintegrant

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ABSTRACT - Purpose: The present study deals with evaluation of crosslinked poly vinyl alcohol (PVA) as a potential disintegrant. **Methods:** Crosslinking of PVA was carried out using glutaraldehyde as a crosslinker, in presence of acidic conditions. The crosslinking reaction was optimized for a) polymer: crosslinker ratio; b) temperature requirement and c) reaction duration. Certain physical parameters of the disintegrant (including sedimentation volume, hydration capacity, specific surface area and bulk and tap density) were determined and compared to the known disintegrants. Characterization was carried out using FT-IR, DSC, XRD, SEM and Photo microscopy studies. The developed excipient was also studied for acute toxicity in rats and found to be safe for oral use. **Results:** Disintegration property of formed product was found to give better results. As compared to known disintegrant (Ac-Di-Sol). The disintegration mechanism of developed disintegrant was postulated based on results obtained from various physical evaluations. Hausner's ratio & Carr's index value of 1.12 and 10.61 suggested excellent flowability. Wetting time and disintegration time of 21.90 ± 0.1 and 26.20 ± 0.2 seconds was obtained at the disintegrant level of 5 % w/w. **Conclusions:** By changing the condition parameters of well known crosslinking reaction of PVA, we obtained a crosslinked product which had excellent disintegration activity, good flow and optimal tableting properties.

INTRODUCTION

In spite of extensive research in the field of modified release dosage forms, conventional tablets for oral ingestion remains the most widely accepted and developed formulations. To ensure high drug availability from such formulations relatively rapid disintegration is one of the pre-requisite. Currently, a class of disintegrants known as super disintegrants (represented by following three categories: crosslinked starch, crosslinked cellulose and crosslinked polyvinyl pyrrolidone) are commonly used in formulation of tablets. Super disintegrants are unique in their own way as they are found to be effective at very low concentrations and yield disintegration time in seconds (1).

Polyvinyl alcohol (PVA) is a well known pharmaceutical excipient used for various purposes. The simplest and the most commonly employed crosslinking reaction involving chemical crosslinking of PVA with glutaraldehyde in presence of acidic conditions has been covered extensively in many research reports (2-3). It has

been reported that chemical crosslinking of PVA can be used as an effective way of producing pharmaceutically safe and useful products (hydrogels, sludge, foam, sponge etc.) for drug delivery (4-7). However, till date none of the reports have been aimed at evaluating the possibility of using chemically crosslinked PVA as a disintegrating agent.

In this study, we have investigated, for the first time, the use of chemically crosslinked PVA as a disintegrating agent. We have found that changing the experimental conditions of well established chemical crosslinking reaction results in a material (hereinafter referred to as CLP), that can be compressed into a tablet, with or without the aid of a binder. The resulting tablet rapidly disintegrates in water, suggesting that CLP can be used as a disintegrating agent, especially in the design and development of fast-disintegrating tablets.

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In this paper, we report the method of preparation of CLP and compare its disintegrating efficiency with known disintegrant i.e. Crosscarmellose (Ac-Di-Sol). Certain physical parameters of the disintegrant were evaluated to obtain an insight into its potential disintegrating efficiency. The study also includes characterization and toxicity evaluation of developed excipient. We have also attempted to postulate a mechanism by which CLP achieves its disintegrating action.

MATERIALS AND METHODS

Materials

Polyvinyl alcohol (PVA), (Mol. wt. 1, 25,000 and a degree of hydrolysis of 97.5-99.5 % mole) was obtained from S.D fine-chem. Limited (Mumbai, India). Hydrochloric acid and glutaraldehyde (25 % w/v) were purchased from Merck Chemical Co. (India). Aceclofenac was kindly supplied by Aarti Drugs (Mumbai, India). Crosscarmellose sodium (Ac-Di-Sol®) and sodium starch glycolate (Primojel®) were obtained from FMC BioPolymer (Philadelphia, PA) and DMV International (Veghel, Netherlands) respectively. Crospovidone (Polyplasdone®) was purchased from Signet Chemicals (Mumbai, India) Dicalcium phosphate dihydrate (Emcompress®) was obtained from JRS Pharma (Patterson, NY). Polyvinyl pyrrolidone (Plasdone K-30®), Milled lactose (Pharmatose® 150M), Sieved lactose (Pharmatose® 50M) and Magnesium stearate were obtained from DMV International (Veghel, Netherlands). Other reagents were analytical grade and double distilled water was used throughout the experiment. For animal studies, Milli-Q water purified using Millipore system (Molsheim, France) was used.

Methods

Cross-linking procedure of PVA

A chemical cross linking reaction utilizing glutaraldehyde was used in this study. Firstly, 5 %, 10 % and 15 % w/v PVA solutions were prepared by dissolving required amount of PVA in hot water at a temperature of 80-90 °C. After cooling the solutions to room temperature, 100 ml of each solution were used for proceeding steps. To above solutions different percentages of glutaraldehyde

solution (2.5-20 % w/v) was added as cross linking agent to obtain a polymer:crosslinker (PVA:GA) ratio ranging from (1:0.5 to 1:1.5 % w/w). The reactants were stirred continuously at 50-60°C for 20-40 mins on a magnetic stirrer (Remi Instrument, India). The above mixture was then poured into different volumes of acidic solution (concentrations varying from 0.1-0.4 N HCl) followed by continuous agitation under constant heating on a magnetic stirrer until the precipitate was obtained. The reaction mixture was then cooled to room temperature and filtered. The white precipitate obtained was washed with water until the filtrate showed a near neutral pH and then subjected to overnight drying (yield > 85 %). The dried product was then passed through sieve no 60 and stored in a dessicator until further use.

Characterization methods

Surface morphology and particle size analysis

The surface morphology of PVA and CLP particles was observed by scanning electron microscopy (Hitachi S-4000 microscope). The samples were loaded on aluminum stubs covered with a double-sided tape. They were then coated with a gold/palladium (60/40) mixture for 4 min in an Emitech K550 coater. Particle size analysis and specific surface area determination was carried out using Malvern Meta-sizer equipped with 2000 Hydro MU.

Fourier-transform infrared (FT-IR) spectroscopy

Fourier transform infrared (FTIR) spectra of the samples were obtained in the range of 400 to 4000 cm^{-1} using a Jasco-FTIR spectrophotometer (Jasco, Essex, UK) by the KBr disc method. Pellets were prepared using a pressure of 14,000 pound for 2 minutes.

Powder X-ray diffractometry

The powder X-ray diffraction (XRD) measurements were conducted over a 10–40° 2 θ range on a Siemens Model D5000 diffractometer, equipped with monochromatic Cu K α ($\alpha_1=1.54060 \text{ \AA}^\circ$, $\alpha_2=1.54438 \text{ \AA}^\circ$) X-rays. The step width was 0.020° 2 θ /min with a time constant of 0.5 s.

Differential Scanning Calorimetry

The samples were subjected to DSC studies using (Perkin Elmer pyris 4 series). Samples were sealed

in 40 µl aluminium pans. An identical empty pan was used as a reference. The samples were scanned at 5 °C/min with a 20 ml/min nitrogen purge.

Moisture content, Sedimentation volume, Bulk & tap density, Carr's Index, Hausner's ratio and Hydration capacity

Moisture content: One gram of accurately weighed sample was subjected to controlled heating at programmed temperature for 5 mins (AND MS-70 moisture analyzer, Japan), the % moisture loss from the sample gave an estimation of moisture content.

Sedimentation volume: Sedimentation volume or the volume of water taken up by gram of sample was determined using reported method (8). Precisely, 1 gm of sample was accurately weighed and transfer to a 10 ml measuring cylinder. The volume of cylinder was made up to 10 ml using distilled water. After keeping it undisturbed for an hour, the liquid was decanted and the volume measured.

Bulk and Tap density: The procedure followed is also referred to as cylinder drop technique. Accurately weighed sample (10 gram) of each disintegrant was introduced into a 10 ml graduated measuring cylinder. The volume occupied by the sample was measured following which the cylinder was subjected to 100 taps and the final volume change was noted down. Bulk density (ρ_{bulk}) and Tap density (ρ_{tap}) was calculated by dividing the weight of sample by volume of untapped and tapped powder respectively.

Carr's index and Hausner's ratio: The Carr's index and the Hausner's ratio were calculated using the equation $[(\rho_{\text{tap}} - \rho_{\text{bulk}}) / \rho_{\text{tap}}] \times 100$ and $\rho_{\text{tap}} / \rho_{\text{bulk}}$, respectively (9-10).

Hydration capacity: The procedure utilized was as follows: 10 ml of water was taken in a petridish and covered with a filter paper such that only the centre of paper touches the surface of water. The filter paper was then allowed to get soaked. The wet paper was then weighed and 100 mg of sample was placed at the centre of the filter paper. It was kept undisturbed for 1 hour followed by reweighing of the paper. Hydration capacity was found out by difference in the weight of paper.

Photo microscopic Studies

Photo microscopic analysis was carried out on both dry and wet samples of disintegrants to study their

swelling behavior. These studies were carried out using Kruss MBL 3100 Inverse microscope equipped with Canon Power Shot S80 digital camera.

Preparation of Tablets

Aceclofenac was used as a hydrophobic active in all tablet formulations. Different batches of tablets were prepared using either lactose (Pharmatose® 50M or 150M) or Di-calcium phosphate (Emcompress® and DCL 11) as fillers; magnesium stearate as lubricant. Disintegrants (CLP, Ac-Di-Sol) were added to the formula at defined concentration (5 % w/w of tablet weight). Tablets corresponding to 450 mg total weight with 100 mg of aceclofenac were prepared either by wet granulation or direct compression on 11 mm flat round punch on single stroke tablet press (CADMACH, India).

To study the effect of varying concentration and hardness on disintegration properties, tablets were prepared with different concentrations of disintegrant (2-5 % w/w of tablet weight) and compressed at hardness ranging from 4-7 kg/cm² (measured using EXPO® Tablet hardness tester EIC-66). Further, to establish a suitable mode of incorporation of the disintegrant, tablets with CLP (5 % w/w of the tablet weight) incorporated either intragranularly, extragranularly or in combined form were prepared and compressed at a hardness of 5 kg/cm².

Evaluation of Tablets

Wetting studies

Wetting studies were carried out according to the reported method (11). In brief, the set up for the study included a set of filter paper band supported on glass petridish filled with water. Tablets for study were placed at the centre of the paper, such that the water absorption occurs only from its lower surface. The time taken for water to reach the centre of the upper surface was noted as wetting time. The readings were taken as average of six observations.

Disintegration studies

The disintegration test was performed in water at 37 °C using a Tablet disintegration apparatus (Electrolab, India). The disintegration times reported are averages of six determinations.

Dissolution studies

Tablets were also subjected to dissolution studies to evaluate the effect of disintegrant on drug dissolution. Dissolution test was carried out using USP XXIV Type II (paddle) apparatus at 37° C; the paddles were rotated at 100 rpm. Dissolution medium was selected as 900 ml (buffer pH 6.8) as aceclofenac shows maximum solubility in buffer pH 6.8 (12). Five milliliter aliquots were withdrawn at intervals of 5, 10, 15, 30 and 45 mins and replaced with 5 ml of fresh medium. The samples were analyzed for aceclofenac content by UV spectroscopy at 275 nm.

Dwell time study

To study the effect of compression time on disintegration property of disintegrant, dwell time study was performed. A 1:1 w/w mixture of CLP and DCP was compressed into a disc using KBr pellet press (Spectrolab, Model SL-89, Mika, Germany) at maximum pressure (3000lb/in²). The disc was subjected to pressure for varying time period (1-5mins). The compressed discs were then evaluated for disintegration test.

Toxicity studies

The developed disintegrant was then evaluated for *in vivo* acute toxicity in rats. The animal requirement was approved by Institute's Animal Ethics Committee (IAEC) and all experiments were conducted as per the norms of Committee for the Purpose of Supervision of Experiments on Animals, India (CPCSEA, India). The test was carried out as per OECD 420 guideline for acute toxicity test using fixed dose procedure [FDP] (13). Male Holzman's rats weighing (250 gms approx.) were selected for study. Three groups of 6 rats each were starved for 24 hours and divided into control and test group. CLP (2000 mg/kg body weight suspended in Milli Q water) was fed orally to test group and control group received normal Milli Q water. The groups were observed for mortality over a period of 14 days.

RESULTS

Optimization of cross linking procedure

Chemical cross linking process used in this study can be used to obtain different kind of products (hydrogels, sponges, slugs or beads) (4-7, 14). In our study the cross linking reaction was optimized in order to get the desired product, the batches of experiments carried out are listed in (Table 1).

It was found that PVA: GA ratio of at least 1:1 w/w or above was required to obtain the desired product. When the reaction was carried out at room temperature RT (25 °C), the product obtained ranged from slugs to hydrogels, which didn't show any disintegrant activity. However, it was observed that by carrying out the reaction at 50-60 °C, white amorphous precipitate was obtained which later showed a very good disintegrant property. Reaction occurred well in the presence of 0.2-0.1 N HCl and 20-30 minutes duration (reaction time) was found to be optimum. Volume of acid also played a crucial role as at lower volume the process failed to give discrete precipitates rather it formed a gelled mass. The drying steps tried in this method included air drying, oven drying and freeze drying. It was seen that air drying resulted in a product with high residual moisture (12 % w/w), which was ineffective in showing any disintegrant property. On the other hand both oven drying and freeze drying gave a completely dry product (2.13 ± 0.09 % w/w and 2.02 ± 0.03 % w/w respectively) with good disintegrant property. It was seen that the freeze dried product was slightly better in terms of disintegrating property which could be attributed to increase in the porosity of the material. Thus, further studies for evaluation of disintegration properties were carried out with freeze dried product.

Characterization studies

Figure 1 shows the SEM images of the raw material and the dried crosslinked products. As seen from the figure, the crosslinked product displayed an amorphous and porous structure as compared to the more crystalline PVA particles. Product dried using freeze drying was found to have more porous and irregular surface as compared to oven dried product.

Table 1. Optimization of cross linking reaction conditions (selected batches)

FORMULA	Batches							
	CLP I	CLP II	CLP III	CLP IV	CLP V	CLP VI	CLP VII	CLP VIII
PVA:GA ratio (w/w)	1:1.5	1:1.5	1:1.5	1:1.5	1:1.5	1:1.25	1:1	1:0.75
Acidic conditions	0.2N HCl	0.2N HCl	0.2N HCl	0.2N HCl	0.1N HCl	0.1N HCl	0.1N HCl	0.1N HCl
Volume of acid (ml)	150	250	250	250	250	250	250	250
Duration of reaction (mins)	5-10	5-10	5-10	20-30	20-30	20-30	20-30	20-30
Temperature	RT	RT	50-60°C	50-60°C	50-60°C	50-60°C	50-60°C	50-60°C

[CLP VII was selected as the optimized batch because of the low GA percentage and relatively milder acidic conditions; CLP VIII was found to be effective, thus proving that PVA: GA ratio of 1:1 w/w or more is required for the formation of desired product]

Average particle size of oven dried and freeze dried CLP was found to be $220.53 \pm 2.01 \mu\text{m}$ and $119.76 \pm 1.58 \mu\text{m}$ respectively. Particle size analysis also gave an estimation of specific surface area (Table 2) which was seen to increase significantly in the product as compared to the raw material. Specific surface area was greater for freeze dried product.

Fourier-transform infrared (FT-IR) spectroscopy was utilized to confirm the crosslinking reaction. FTIR spectrum of pure PVA sample (Figure 2 A) clearly reveals the major peaks associated with poly vinyl alcohol. For instance, C-H broad alkyl stretching band ($\nu = 2850\text{-}3000 \text{ cm}^{-1}$) and typical strong hydroxyl bands for free alcohol (non bonded -OH stretching band at $\nu = 3600\text{-}3650 \text{ cm}^{-1}$), and hydrogen bonded band ($\nu = 3200\text{-}3570 \text{ cm}^{-1}$) (15). FTIR spectrum in Figure 2B is associated with CLP (PVA cross linked by glutaraldehyde). It can be observed that two important peaks at $\nu = 2870$ and 2720 cm^{-1} of C-H stretching are related to aldehydes, a duplet absorption with peaks attributed to the alkyl chain (15-16). It was also seen that the O-H stretching vibration peak ($\nu = 3330\text{-}3350 \text{ cm}^{-1}$) was decreased when compared to pure PVA. This result suggests that the hydrogen bonding becomes weaker in cross linked PVA compared to pure PVA because of the reduction in the number of OH groups due to acetal

formation (2). It was observed that there was no major increase in the C=O band at approximately $\nu = 1715 \text{ cm}^{-1}$ indicating that the aldehyde groups of GA was almost completely used up in the cross linking reaction with O-H groups of PVA chain. In addition, the C-O stretching at approximately 1100 cm^{-1} in pure PVA is replaced by a broader absorption band (from $\nu = 980$ to 1110 cm^{-1}), which can be attributed to the ether (C-O) and the acetal ring (C-O-C) bands formed by the cross linking reaction of PVA with GA (2). Thus, it was assumed that CLP was a crosslinked product of PVA, formed by chemical crosslinking of glutaraldehyde with PVA. Figure 3 presents the XRD patterns of PVA and CLP (oven dried and freeze dried). The characteristic peaks of PVA at 19.71 , 20 and $23.32^\circ 2\theta$ were absent in the diffractograms of CLP.

DSC thermograms of samples are shown in figure 4. As seen from the figure, PVA shows two characteristic peak at around $100\text{-}120$ and $190\text{-}220^\circ\text{C}$. The peak at around $100\text{-}120^\circ\text{C}$ represents the evaporation of residual water present in the sample. The sharp peak at approximately 230°C represents the melting of PVA. On comparing the DSC thermogram of CLP to PVA both these peaks were found to disappear. CLP was found to show a new peak at $80\text{-}90^\circ\text{C}$, which could be attributed to the softening point of the formed crosslinked product.

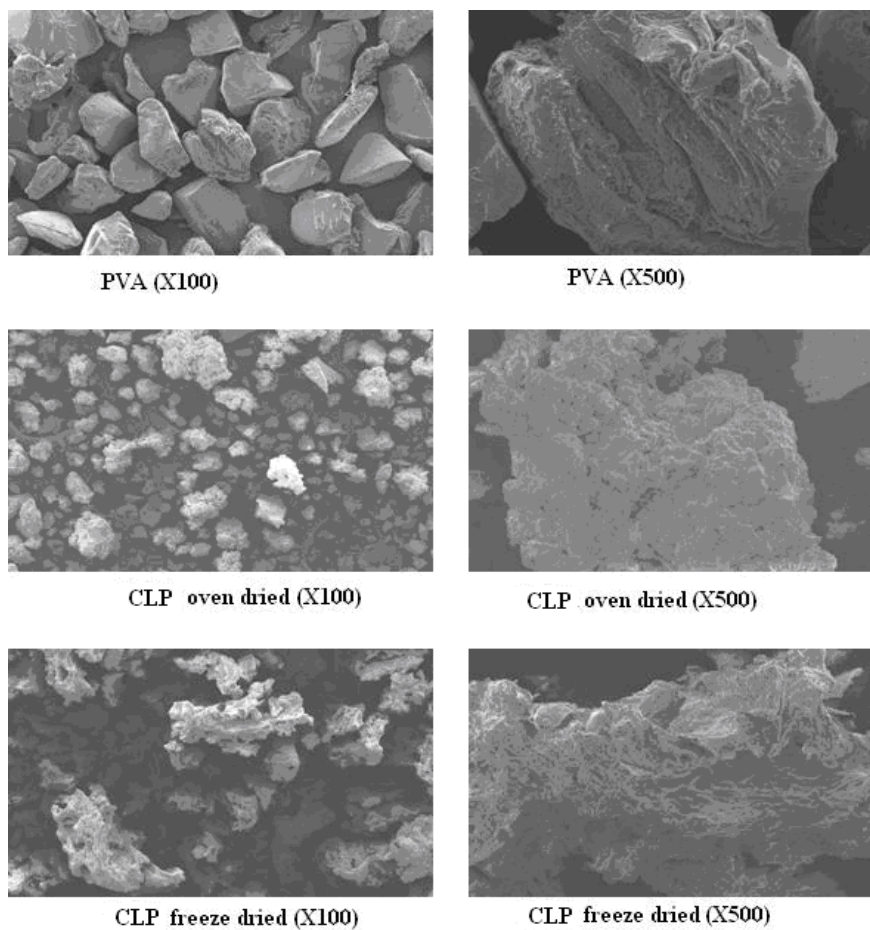


Figure 1. SEM images of PVA, CLP oven dried and CLP freeze dried

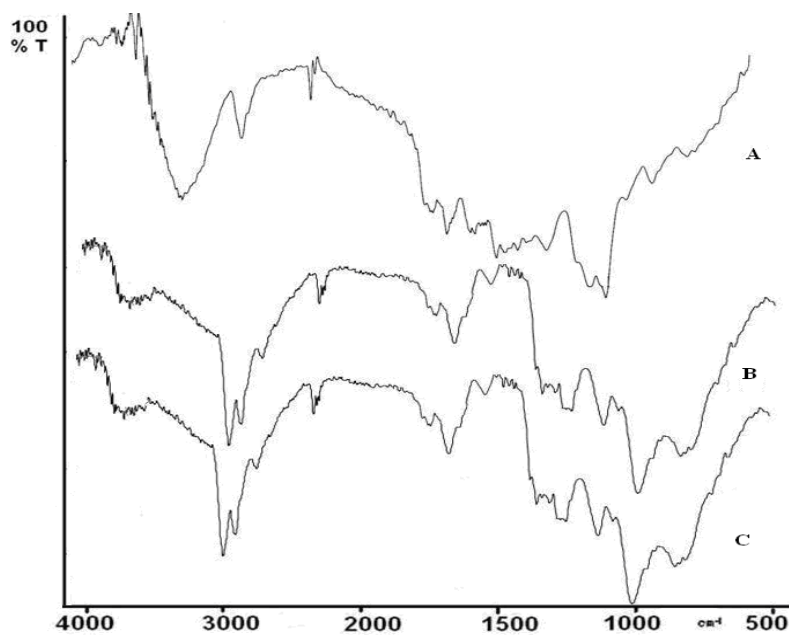


Figure 2. FTIR spectra of A] PVA and B] CLP freeze dried and C] CLP oven dried

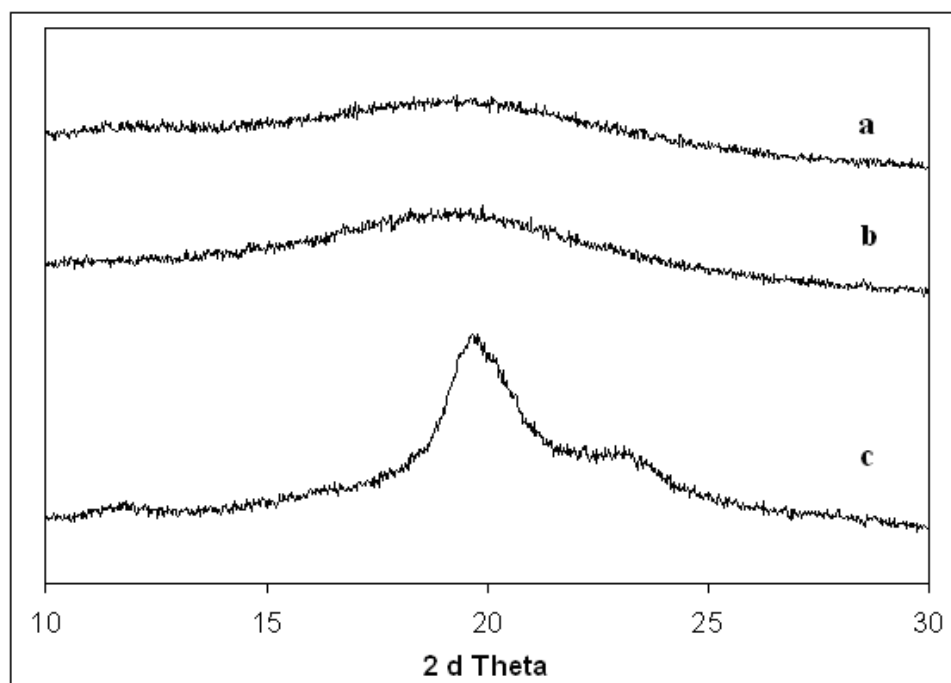


Figure 3. X-RD patterns of a] PVA; b] CLP oven dried and c] CLP Freeze dried

Table 2. Particle size and specific surface area of oven dried and freeze dried CLP.

Parameters	Oven dried CLP			Freeze dried CLP		
	I	II	III	I	II	III
Particle size (μm)	222.4	218.1	220.8	118.4	119.4	121.5
Mean $\pm$ S.D		220.53 $\pm$ 2.01			119.76 $\pm$ 1.58	
Specific surface area (m^2/g)	0.0314	0.0324	0.0301	0.481	0.486	0.457
Mean $\pm$ S.D		0.0313 $\pm$ 0.0011			0.474 $\pm$ 0.015	

Figure 5 shows photomicroscopic slides of CLP, Ac-Di-Sol, SSG and crospovidone in both dry state and wet state. As seen from the results (Figure 5), CLP showed negligible swelling and discreteness of particles in wet state as compared to both Ac-Di-Sol and SSG. The results of this study are in good agreement with the sedimentation volume and hydration capacity studies.

Evaluation of physical properties

The developed product CLP (freeze dried) was subjected to evaluation test for physical properties and results of same were compared with that of Ac-Di-Sol, SSG and crospovidone. Results obtained

from the evaluation studies are given in Table 3. Hausner's ratio and the Carr index have been widely used to estimate the flow properties of powders. A Hausner's ratio of less than 1.20 is indicative of good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow display by the material (17). The Carr index values of 5–10, 12–16, 18–21, and 23–28 indicate excellent, good, fair, and poor flow properties of the material, respectively (9). Thus from the obtained values of Hausner's ratio and the Carr index, it can be suggested that CLP possesses excellent flow properties.

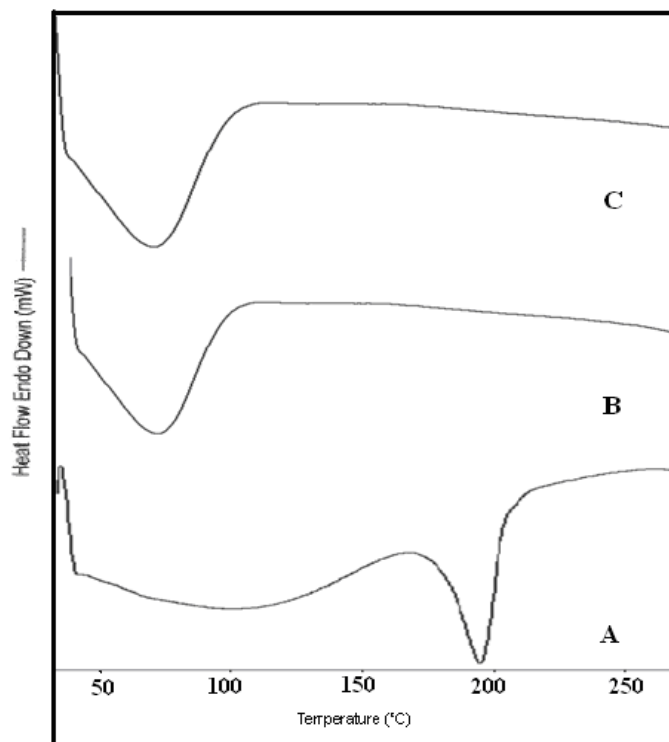


Figure 4. DSC thermo grams of A] PVA; B] CLP oven dried and C] CLP freeze dried

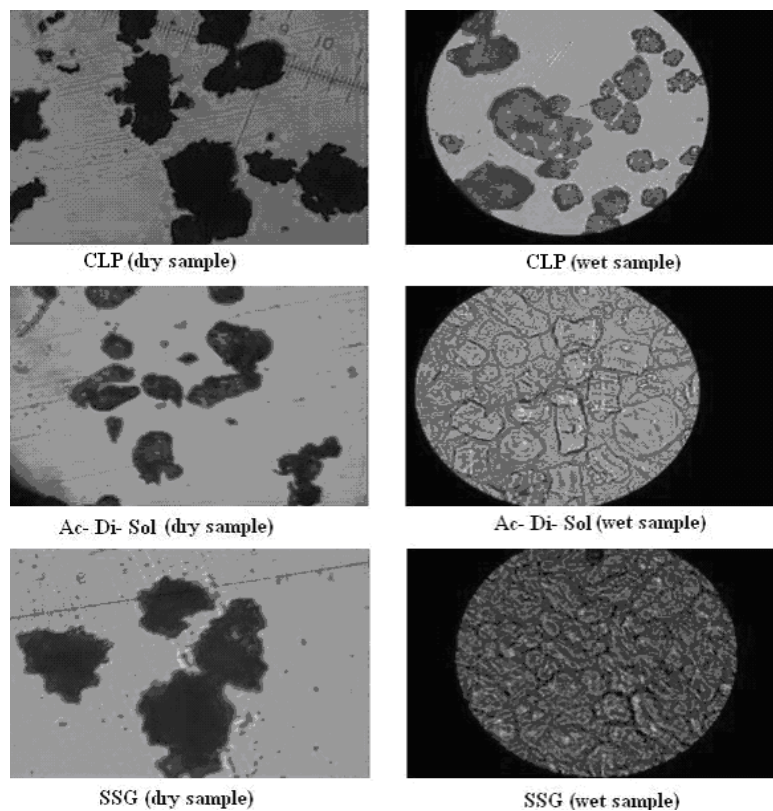


Figure 5. Photomicrographs of CLP, Ac-Di-Sol and SSG in both dry form and wet form

Table 3. Comparative powder properties of disintegrants

Properties	CLP freeze dried Mean (S.D.)	Ac-Di-Sol Mean (S.D.)	SSG Mean (S.D.)	Crospovidone Mean (S.D.)
Moisture content (%w/w)	1.13 (0.09)	2.627 (0.12)	11.214 (0.158)	8.011 (0.052)
Sedimentation volume (ml/g)	4.93 (0.2516)	20.16 (1.2683)	29.9 (1.1532)	18.2 (1.0520)
Bulk density (g/ml)	0.449 (0.001)	0.624 (0.003)	0.646 (0.001)	0.536 (0.009)
Tap density (g/ml)	0.502 (0.001)	0.834 (0.002)	0.957 (0.002)	0.665 (0.003)
Carr's index	10.61	25.14	32.42	19.39
Hausner ratio	1.12	1.34	1.48	1.24
Hydration capacity (%)	1.58 (0.010)	7.32 (0.016)	9.10 (0.09)	5.43 (0.11)

Disintegration properties

Batches of experiments were conducted to evaluate the disintegration properties of CLP (freeze dried). Tablets with constant target weight (450 mg) were prepared using various concentration of disintegrant at different hardness; other parameters were also varied in order to evaluate its disintegration property. Ac-Di-Sol is considered to be better in terms of performance as compared to SSG and Crospovidone (18) and in our preliminary study; tablets with Ac-Di-Sol gave the better results as compared to SSG and Crospovidone. Thus, tablets with Ac-Di-Sol at same concentrations as CLP were used as control for comparison purpose. Tablets prepared using wet granulation gave a better result as compared to direct compression and thus wet granulation was chosen as method of choice. It was observed that the disintegration property of CLP was unaffected by the type of filler used in the formulation as it gave similar disintegration time for tablets with either hydrophilic filler (Lactose) or hydrophobic filler (Di-calcium Phosphate). It was also observed that the mode of incorporation of disintegrant in the tablet showed a profound effect on the disintegration time (Table 4), extragranular addition proved to be ideal as it was seen that tablets with just intragranular addition or addition at both intra and extra granular level did not give a satisfactory result.

Figures 6-7 display the results of disintegration test and wetting studies. As seen from the figures, CLP appears to be an interesting disintegrant. The disintegrant was found to be effective at all concentration ranging from 2-5 % w/w. Further, it was also seen that tablet compressed at higher hardness took longer time to get wet. However, the

disintegration time was surprisingly found to decrease with increase in the hardness.

Dwell time study

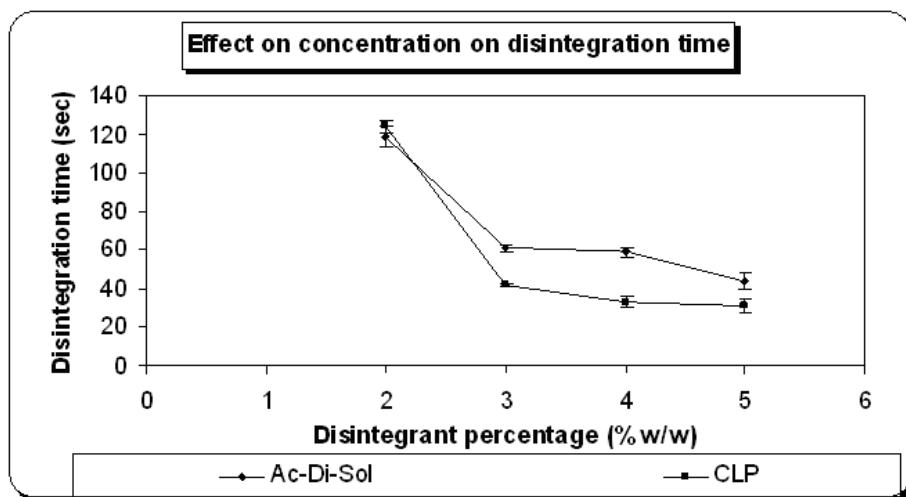
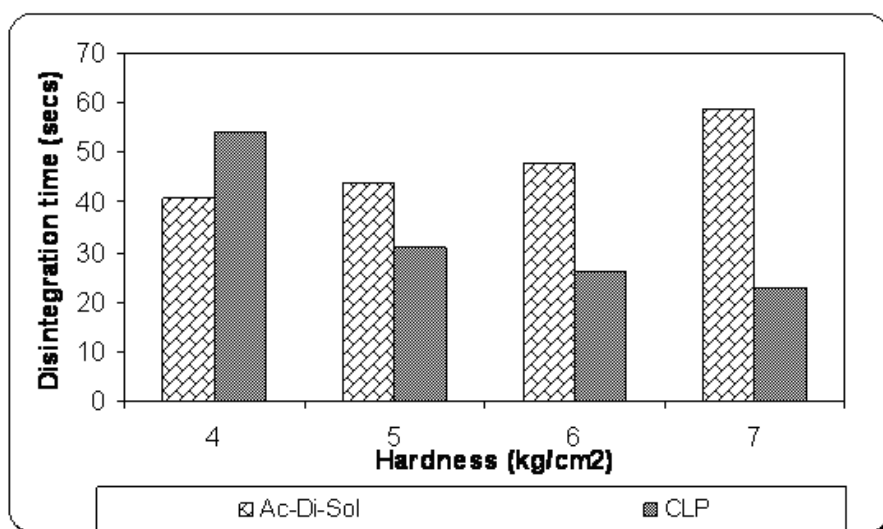
It was observed that the disintegration of the disc was affected with the time as the disintegration time was seen to decrease with the increase in the exposure time of compression pressure (Figure 8). The reason for this observation can be attributed to the fact that when the compression pressure is applied to the particles they undergo plastic deformation which is a time dependent process. Thus, increasing the exposure time leads to proportional increase in the plastic deformation of particles (19).

In vitro dissolution

To ascertain the overall acceptability of a disintegrant, it must be shown that no interference with the dissolution behavior of drug from the tablet is involved (20). Ac-Di-Sol is known to disintegrate the tablet into fine particles and consequently results in an increase in the drug release. To investigate the effect of CLP (freeze dried) on drug release, tablets without any disintegrants and with CLP and Ac-Di-Sol (5 % w/w) were subjected to invitro dissolution studies. Figure 9 shows the comparative release profile of tablets. As seen from the figure, the release of drug was enhanced as compared to tablet without any disintegrant and tablets with CLP and Ac-Di-Sol gave almost similar release profiles. Thus it can be claimed that the disintegration mechanism of CLP results in generation of fine particles with enhanced exposed area for medium interaction as is seen with Ac-Di-Sol.

Table 4. Effect of mode of incorporation of disintegrant on wetting time and disintegration time

Mode of Incorporation	Total Disintegrant added (% w/w)	Wetting time (sec)	Disintegration Time (sec)
Extragranular only	2	118.6 ± 1.8	123.9 ± 1.7
	3	40.70 ± 1.4	42.30 ± 1.6
	4	31.70 ± 0.3	33.20 ± 0.4
	5	21.90 ± 0.1	26.20 ± 0.2
Intra & Extra granular	2	227.3 ± 2.2	248.2 ± 2.8
	3	137.4 ± 2.2	138.4 ± 2.1
	4	109.4 ± 0.5	117.2 ± 1.8
	5	97.80 ± 0.8	100.2 ± 2.2
Intra granular only	2	348.9 ± 3.2	356.2 ± 1.1
	3	256.7 ± 2.7	294.5 ± 3.2
	4	198.7 ± 4.1	247.3 ± 4.7
	5	149.6 ± 1.2	180.9 ± 2.4

**Figure 6a.** Disintegration test for tablets containing different percentages of disintegrates compressed at hardness of 5 kg/cm²**Figure 6b.** Effect of hardness on disintegration time of tablets with disintegrants (5 % w/w)

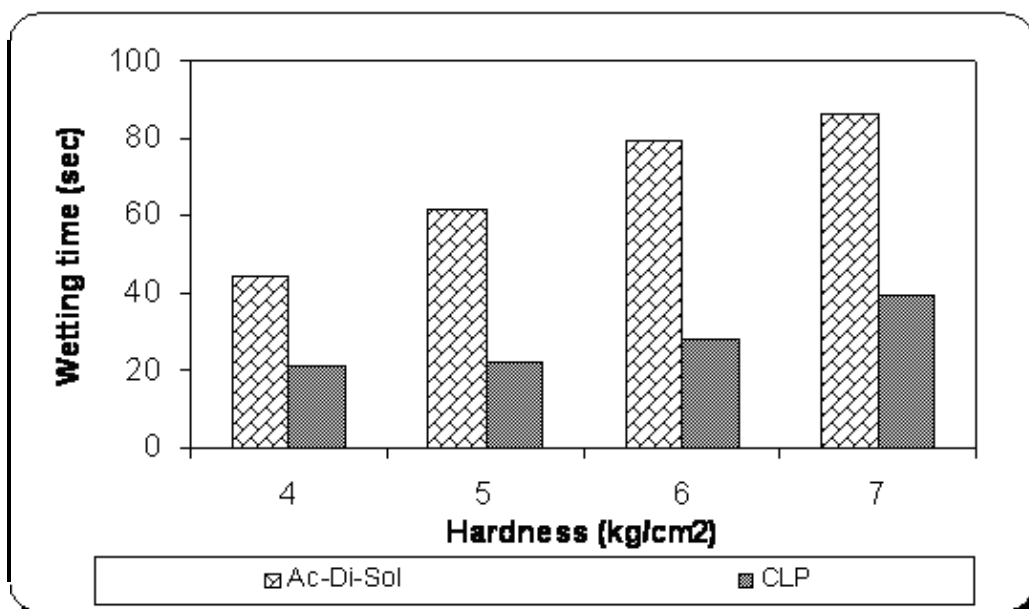


Figure 7a. Wetting test for tablets containing different percentages of disintegrants compressed at hardness of 5 kg/cm²

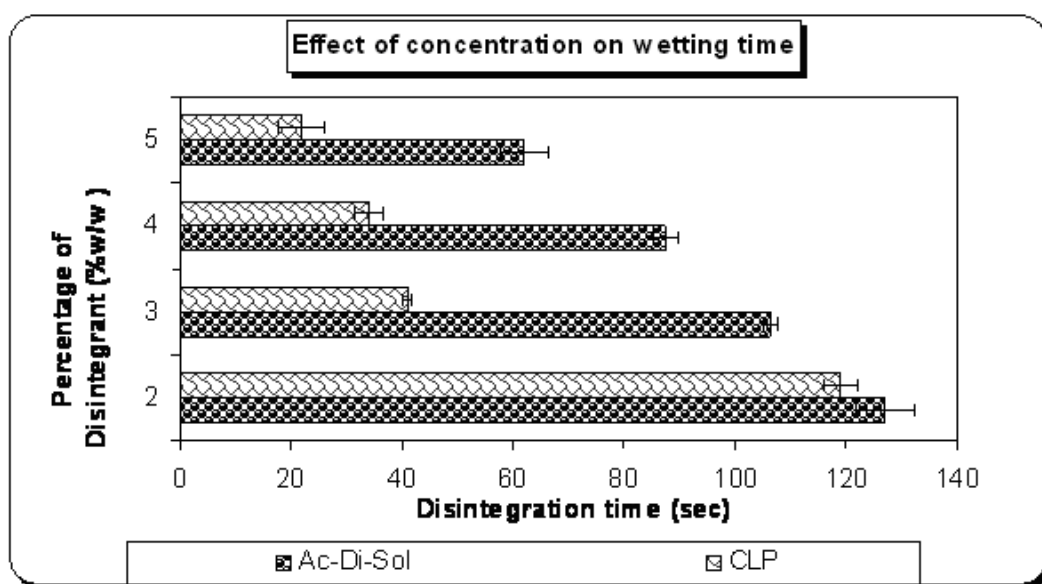


Figure 7b. Effect of hardness on wetting time of tablets with disintegrants (5 % w/w)

In-vivo toxicity

At the end of 14 days, a 100 % survival without any evident toxicity was observed. Thus, it can be assumed that the oral LD₅₀ is likely to be above

2000 mg/kg body weight and therefore the developed disintegrant (CLP) can be considered as safe for oral use (13).

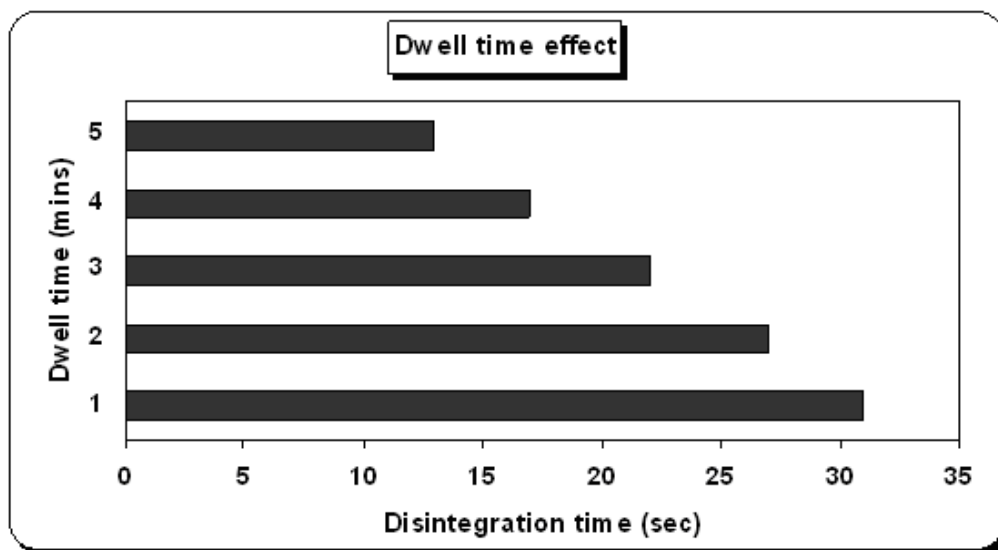


Figure 8. Effect of dwell time on disintegration behavior

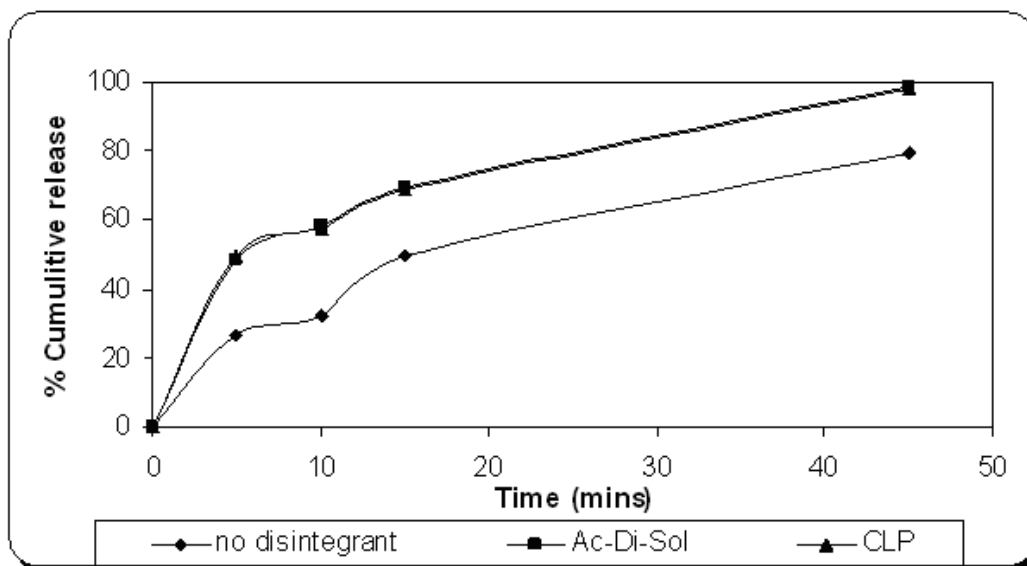


Figure 9. Drug release profile of tablets without disintegrant and with CLP and Ac-Di-Sol (5 % w/w)

DISCUSSION

It could be suggested that the process used in the current work resulted in formation of a crosslinked product with high hydrophobicity and good flow

and excellent disintegration property. The crosslinking of PVA by glutaraldehyde was confirmed from the detailed interpretation of FT-IR

spectra as discussed in the results section. The change in the physical form of prepared substance was confirmed by the data obtained from DSC, XRD and SEM studies.

Also, it can be seen from figure 3 that the mode of drying had no effect on the XRD patterns as both oven dried and freeze dried product showed similar diffraction pattern. The disappearance of characteristic peaks and flatter diffractograms of CLP can be attributed to the amorphous nature of crosslinked product.

Owing to its porous structure CLP was found to show low bulk and tap density (Table 3). Also, the porous structure of formed product was prominent from the SEM images (Figure 1). The low % moisture content could be attributed to relatively hydrophobic nature of CLP, resulting in lower residual moisture. The lower value for sedimentation volume and hydration capacity also suggests the limited swelling potential of CLP as compared to Ac-Di-Sol, SSG and Crospovidone. Moreover, Hausner's ratio & Carr's index value of 1.12 and 10.61 (Table 3) suggested excellent flowability of the formed disintegrant.

An attempt was made to postulate the mode of action responsible for the disintegrating property of CLP. Results from the physical evaluation studies (lower values of hydration capacity and sedimentation volume) suggested an absence of swelling of CLP. Moreover, photomicroscopic studies (Figure 5) further confirmed that the developed disintegrant did not show any profound swelling and thus it can be stated that the disintegrating property of CLP was due some other mechanism. Results from wetting studies (Figure 7a and 7b), showed that CLP promoted wetting of the tablet suggesting that wicking is one of the predominant mechanisms responsible for the disintegration activity. The large specific surface area and porous morphology further ascertains wicking potentials of the developed disintegrant.

Further, it was seen that inclusion of water soluble filler resulted in an increase in the wetting time which was quite obvious as it could be attributed to the absorption of water by hydrophilic filler thereby leading to an alteration in channel for water uptake (21). However, it was seen that the presence of hydrophilic filler had no effect on disintegration. Moreover, it was also seen that tablets compressed at higher pressure resulted in faster disintegration. It is well known that wicking

action is dependent on the porosity of the tablet which in turn is inversely proportional to the hardness of the tablet, thus the increase in hardness results in less porous tablets which in turn limits the wicking action (22). But in our case the disintegration time was not affected by the increased hardness. Thus, it was concluded that wicking alone was not responsible for the disintegrating property.

At this point, the decrease in the disintegration time at higher hardness was assumed as a justification for mechanical phenomenon of particle deformation. It is well known that at higher compression force the deformation of particles can display a greater disruptive force upon contact with the penetrating liquid resulting in faster disintegration (23). In fact, it has already been demonstrated that deformation of starch grains is one mode by which starch affects the disintegration (24). Thus, we can assume that particle deformation/reformation is also responsible for the disintegration effect. Results from dwell time (Figure 8) study further supports our above claim as particle deformation or plastic deformation is a time dependent process and it can be assumed that the greater deformation would lead to an equivalently quicker reformation leading to faster rupture of compressed mass. Thus, it was postulated that the mechanism of disintegration in this case consequently appears to be governed by wicking action and mechanical phenomenon i.e. deformation of disintegrant particles.

CONCLUSION

The developed excipient CLP was found to have excellent disintegration properties comparable to known disintegrant (Ac-Di-Sol). The disintegrant was found to be effective at a concentration ranging from 2-5 % w/w and it also showed no untoward effect on drug dissolution. The mechanism of disintegrant was postulated as the one govern by wicking action and mechanical phenomenon of particle deformation. In vivo toxicity studies proved that the developed disintegrant is orally safe. In conclusion, the results provided here suggest that CLP has the potential to be used as an effective disintegrating agent.

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