Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 4, 2012

Research Article

A CONCEPT PROOF OF POTENTIAL OF EXPERIMENTAL DRIED MUCILAGE ISOLATED FROM THE SEEDS OF *OCIMUM BASILICUM* AS A DISINTEGRANT

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Received: 06 July 2012, Revised and Accepted: 13 Aug 2012

ABSTRACT

In an attempt to avoid complexities associated with development of synthetic and semi synthetic excipients, comparatively less explored area of herbal products was tried. The present investigation was undertaken with a view to develop fast disintegrating tablet of Paracetamol using dried mucilage (DM) prepared by drying the mucilage isolated from the seeds of *Ocimum basilicum* as novel disintegrating agent. Selection of dried mucilage as a novel excipients can be justified because of its desired functionality. The fast disintegrating tablets of paracetamol were prepared by adopting conventional wet granulation technology. The tablets were evaluated for characteristics such as weight variation, crushing strength, disintegration time and dissolution rate and compared with characteristics of fast disintegrating tablets of paracetamol prepared by using established disintegrants crosscarmellose sodium, crosspovidone and sodium starch glycolate. Fast disintegrating formulations prepared by using established disintegrants and dried mucilage as novel disintegrating agent exhibited fast disintegration of tablets followed by dissolution of the active (paracetamol).There was no sign of interaction between the dried mucilage and paracetamol as revealed in results of preliminary interaction studies. The statistical analysis of experimental data of disintegration studies suggested that Paracetamol tablets prepared by using dried mucilage as disintegrating agent resulted in rapid disintegration of the tablet comparable to established disintegrants.

Keywords: *Ocimum basilicum,* Mucilage.

INTRODUCTION

Recent developments in the technology have prompted scientists to develop fast disintegrating tablets which improved patient compliance and convenience. Fast disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. The importance of quick tablet disintegration and dissolution to ensure rapid availability of active ingredient(s) for absorption is well recognized [1-2]. The plain starches were the most widely used disintegrants but could not be used in low concentrations to effectively break apart the tablet. The compendial standards for fast disintegrating tablets are considerably shorter than conventional compressed tablets. Only a few acceptable disintegrants are currently available to pharmaceutical scientists. Hence there is a need for continuous search for new disintegrating agents [3-6]. Wicking and swelling were found to be the primary and considered to be most important mechanisms of action for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas etc., may play a role in particular cases of tablet disintegration [7,8]. The mucilage isolated from various plants belonging to family Ocimum were tried for their disintegrating properties [9-11]. Mucilage was isolated from the seeds of *Ocimum basilicum* adopting the procedure described in our earlier paper, dried and used in the present study as dried mucilage (DM) [12]. Its swelling index was found to be 40% which was much better than crosscarmellose (10%), Crosspovidone (10%), and sodium starch glycolate (25%) used in this study [13]. The excellent water uptake and swelling properties exhibited by dried mucilage impelled us to investigate its disintegrating properties. Despite of the fact that various parts of the herb *Ocimum basilicum* as a whole or their extracts had been thoroughly studied for therapeutic and dietary applications; this plant is rarely exploited for its pharmaceutical applications. Conceding the need to develop new excipients, according to the proceedings of sessions conducted related to functionality testing of excipients, a flexible approach would be adopted that attempts to consider functionality of the excipients with its safety profile [14]. The composition of this mucilage isolated in a similar way as adopted in the present study from the seeds of *Ocimum basilicum* is reported and constitutes two major fractions of glucomannan (43%) and 1-4 xylan (24.29%) and a minor fraction of glucan (2.31%) [15]. These seeds are being consumed for years together as a food ingredient in beverages (Sharbats) and ice desserts (faludas) in many parts of Asia. The IPEC had proposed guidelines for the extent of testing required for any new excipient like the dried mucilage in the present study which is a chemical entity already being used as food ingredient [16]. According to them after physicochemical characterization of such new excipient one should proceed for its functionality testing which was the main purpose of this study.

There have been some methods available to prepare the rapidly disintegrating tablet. However, these methods required the particular machines and the time consuming techniques. Moreover, it is reported that the hardness of these products was not enough to stand up to process of packaging and transportation and thus higher costs [17, 18]. Therefore, conventional compression was thought to be the convenient and cheap way to produce tablets with sufficient structural integrity and followed in the study. Paracetamol was selected as a model drug since it is an extremely widely used analgesic and antipyretic. The commercially available and thermodynamically stable form of paracetamol is form I (monoclinic) that exhibits poor compressibility and processibility. Thus it provides an interesting system for studying the effects of processing and formulation variables particularly to test the functionality of novel excipient [19, 20].The purpose of the current study was to evaluate the functionality of dried mucilage (DM) prepared by drying the mucilage isolated from the seeds of *Ocimum basilicum* as a tablet disintegrant in fast disintegrating tablet formulation of Paracetamol in comparison with three established disintegrants, i.e. Crosscarmellose sodium, crosspovidone and sodium starch glycolate and to study the dissolution characteristics of fast disintegrating tablets.

Paracetamol was obtained as a gift sample from Shrikrishna Pharma. Ltd. Crosscarmellose sodium (Ac-Di-Sol), Sodium starch glycolate (Primojel), Crosspovidone (Polyplasdone, XL-10-ISP) were received as gift samples from Lupin Research Park, Pune. Microcrystalline cellulose and starch were purchased from commercial source. The dried mucilage was prepared after isolation from authenticated seeds of *Ocimum basilicum* by the method reported earlier by us and a patent for it is pending [12]. In brief the seeds were soaked in deminerlised water in a proportion 1:20 for 2 hrs. The mucilage forming component present in the pericarp of the seeds immediately swelled. Then the whole mass was homogenized and centrifuged to separate the mucilage from seeds. It was dried and stored until use. It is referred as dried mucilage (DM- new excipient) in this paper. Since this method of isolation involved only water as a solvent, there

was no possibility of presence of residual organic solvent. To determine the swelling index, one gram of dried mucilage was taken in a 25 mL ground glass water cylinder graduated over a height of 25 ml in 0.5 mL divisions. To this 10 mL water was added and this was shaken occasionally for 1 hr. and then allowed to stand for 24 hr. The volume occupied by swollen mass was measured and the swelling index was calculated by the formula- SI= Xt-Xo /Xo ×100. Where Xt is final volume occupied by swollen mass and Xo is initial volume of dispersion of superdisintegrant and water.

The preliminary interaction study of dried mucilage and paracetamol was done by Fourier transform infra red spectroscopy (FTIR),Differential scanning calorimetry (DSC) and X ray difractometry of 1:1 physical mixture of dried mucilage and paracetamol. Fourier transform infrared (FT-IR) spectroscopy was employed in the solid state on an FT-IR 8400S Shimadzu, Japan. The instrument was operated under dry air purge and the spectra were scanned over a frequency range 4000–500 cm^{-1} with a resolution of 4 cm^{-1}. DSC study was performed using DSC (TA4000, Mettler, and Japan) apparatus. Samples (5–10mg) of paracetamol and DM (new excipient) were weighed and sealed into the aluminum pan. DSC runs were conducted over a temperature range of 40- 200^{o}C at a rate of 10^{o}C/min. Powder X-ray diffraction measurement XRD measurement was performed using a powder X-ray diffractometer(Barker AXS D-8 Advance, Germany) with Ni-filtered, Cu (λ=1.54060A^{0}) radiation. The entrance slit was 0.60mm.The diffraction pattern was measured with a voltage of 40kV and a current of 40mA over a 2θ range of 2.5–40^{0} in a step scan mode (step interval of 0.01^{o} and 1step/sec.)

Granules were prepared for formulations F1, F2, F3 and F4 of composition reported in Table 1 by wet granulation using isopropyl alcohol as a binder. The granules were screened with 18 number sieve and then 20 number sieve was used for dry screening. The granules were compressed into tablets using a mini rotary tablet press (Minipress-II- MT) with 8mm punches at constant pressure. Tablet disintegration time was measured in 900 mL of 0.1N HCl using modified USP apparatus II by adopting the procedure as suggested by Bi et al 1996 and Sunanda H et al 2002 [21, 22]. The dissolution study of tablets (from F1, F2, F3 and F4 formulations) was performed in United States Pharmacopeia (USP) dissolution test apparatus II (TDT-08L, Elecrolab, Mumbai, India). The dissolution medium used was 900 mL of buffer pH 1.2 at 37°C ± 2°C. The paddle speed was 100 rpm. Samples were collected at predetermined time intervals, sufficiently diluted and analyzed on multicomponent mode; spectrophotometrically at 243.0 nm for paracetamol. Percent drug release of paracetamol after 15 minutes time interval was determined and reported here for all the formulations. The significance of differences between formulations F1, F2, F3 (prepared by using established disintegrants and F4(prepared by using DM) with respect to their disintegration time was assessed by analysis of variance, followed by Bonferroni multiple comparison test using Graph Pad Prism Version 4 software (Graph Pad Software, Inc.).

Table 1: Composition of paracetamol fast disintegrating tablet formulations.

Formulation	Ingredients (mg/tablet)							Results*	
	Paracetamol	Micro crystalline cellulose	Starch	Sodium starch glycolate	Cross povidone	Cross carmellose	Dried mucilage	Disintegration time Sec (n=6)	Drug release % (t_{15}) (n=3)
F1	150	50	20	20	-	-	-	27.5±0.55	95.175±4.51
F2	150	50	20	-	20	-	-	36.83±1.94	89.225±4.5
F3	150	50	20	-	-	20	-	45.5±2.66	82.045±1.5
F4	150	50	20	-	-	-	20	18.66±2.34	99.059±2.1

* All values indicate mean ± SD

All the principle peaks of paracetamol were retained (at 1653 cm^{-1} due to C=O stretching, peaks due to aromatic vibrations from 1450 cm^{-1} -1600 cm^{-1} etc.) in FTIR spectrum of 1:1 physical mixture of paracetamol and dried mucilage (FTIR spectrum is not shown here). Thermal analyses were carried out on single components and the binary physical mixtures of drug/excipient to check purity of the drug and to reveal any possible interactions as reported in Fig 1. The thermogram of dried mucilage exhibited broad endotherm below 100^{0} C which might be due to vaporization of water associated with the dried mucilage. Paracetamol presented a narrow and symmetric melting endotherm, peaking at 169^{0}C both as a single entity and in physical mixture as well. The binary mixture of dried mucilage and paracetamol showed no significant change in the FTIR spectrum and thermogram. Thus there was no evidence of interaction between the DM (new excipient) and the paracetamol. There was marked reduction in peak intensities in PXRD spectrum of paracetamol when presented in the form of a physical mixture with dried mucilage (Fig 2).

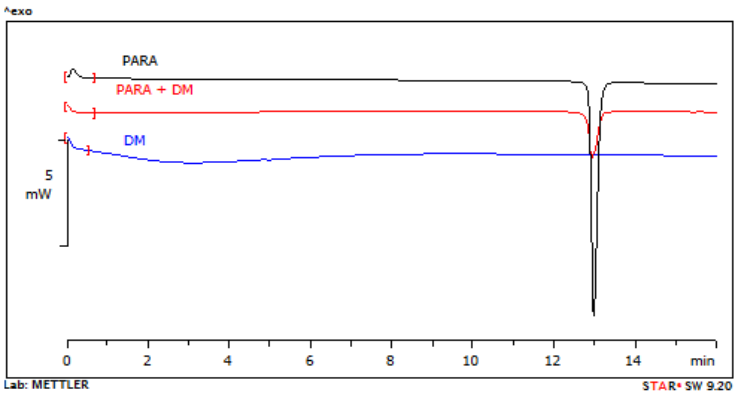

Fig. 1: Overlay of DSC thermograms of Paracetmol, Physical mixture (Paracetamol: DM; 1:1) and Dried mucilage (DM).

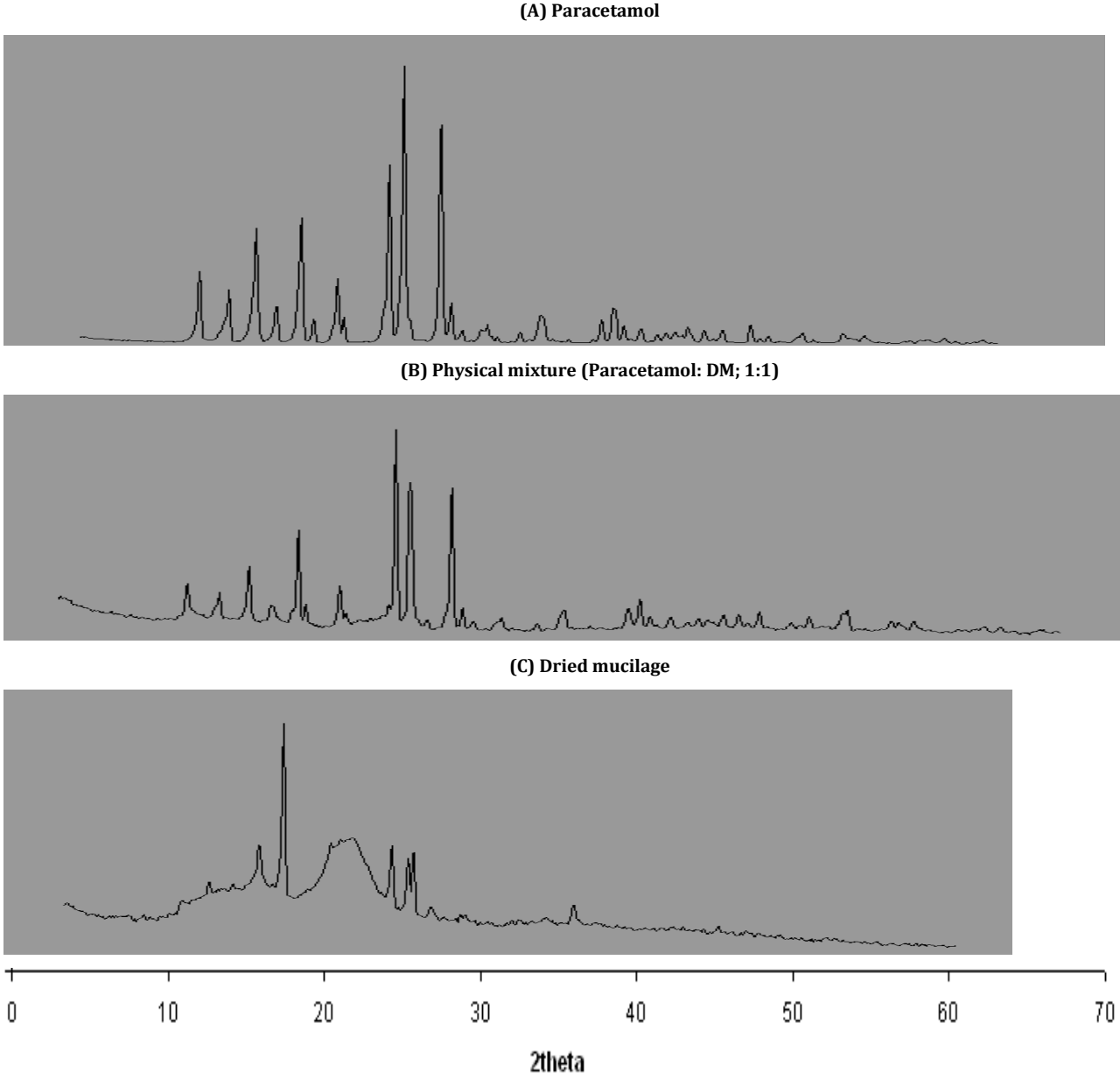

Fig. 2: PXRD patterns of (A) Paracetamol, (B) Physical mixture (Paracetamol: DM; 1:1) and (C) dried mucilage (DM).

The results of analysis of X-ray diffraction patterns of Paracetamol indicated that molecular dispersion of Paracetamol in dried mucilage resulted in a marked decrease in the crystallinity of Paracetamol. This suggestion was further supported by the results of dissolution studies. The results of disintegration time and dissolution studies are reported in Table1. The disintegration time data for all the formulations was statistically analyzed by applying One way ANOVA followed by Bonferroni test. Differences were considered to be statistically significant for $P < 0.001$.The results of statistical analysis are depicted in Table 2.

Table 2: Summary of one way anova followed by bonferroni's multiple comparison tests for disintegration time

Bonferroni Multiple Comparison Test	Mean Diff.	t	Significant p<0.001	99.9%C.I. of Diff.
F1 vs. F4	8.833	7.503	Yes	3.748 to 13.92
F2 vs. F4	18.17	15.43	Yes	13.08 to 23.25
F3 vs. F4	26.83	22.79	Yes	21.75 to 31.92

Ideally ingredients that are used in the formulation of fast disintegrating and dissolving tablets should allow quick release of the drug, resulting in faster dissolution. The least disintegration time of the tablets containing dried mucilage (DM) clearly explains its efficiency as a disintegrant. This is because of its highest swelling index as compared to other disintegrants used in the present study. Dissolution serves as a key and control test in fast disintegrating tablets product development. This is very important, because if the fast disintegration does not followed by fast dissolution of a drug; the purpose of the entire experiment would not have been served appropriately. The fast disintegrating tablet of paracetamol formulated using dried mucilage exhibited maximum average percent drug release after15 minutes. This observation was in accordance with the reported fact that the inclusion of disintegrants

or superdisintegrants in the formulation improved dissolution of a drug [23- 25].The disintegration time data was statistically analyzed by Bonferroni multiple comparison tests. The differences in the disintegration time of the formulations were found to be statistically significant at $p<0.001$. Thus reduction in disintegration time of formulation prepared by using dried mucilage as a new excipient was statistically significant than the disintegration time of formulation prepared by using the established disintegrants.

Fast disintegrating tablets of paracetamol were prepared using dried mucilage as novel disintegrating agent and following conventional wet granulation technology. The desired functionality of the dried mucilage was due to its high swelling index. The disintegrating ability of dried mucilage was comparable to the established disintegrants, i.e. croscarmellose sodium, crospovidone, and sodium starch glycolate. Thus this new excipient demands its well planned investigation; as it may acquire GRAS status if cautious efforts are taken.

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