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Research Article

Studies on Orally Disintegrating Tablets Prepared by Using Natural and Synthetic Superdisintegrants

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ABSTRACT
The objective of present study was to compare the disintegration efficiency of mucilage isolated from *Plantago ovata* with commonly used synthetic superdisintegrant, croscarmellose sodium in the formulation of orally disintegrating tablets. Effects of varying concentration of both superdisintegrants on disintegration time were studied. Orally disintegrating tablets of metoclopramide hydrochloride were prepared using selected superdisintegrants by direct compression technique. Prepared tablets were evaluated for weight variation, thickness, hardness, friability, disintegration time, wetting time, water absorption ratio and dissolution test. Swelling index was also investigated for comparing the swelling property of croscarmellose sodium with mucilage of *Plantago ovata*. Swelling index of mucilage isolated from *Plantago ovata* was found to be greater (94 ± 2.5% v/v) when compared with croscarmellose sodium (85 ± 1.5% v/v). The present study indicated that mucilage isolated from natural source proved to be more effective for their disintegrating property than the most commonly used synthetic superdisintegrant, croscarmellose sodium.

Keywords: Orally disintegrating tablets, direct compression, croscarmellose sodium, *Plantago ovata* mucilage powder.

INTRODUCTION

The demand for orally disintegrating tablets (ODTs) has been growing since the last 2-3 decades especially for the patients who have swallowing difficulties. Due to decline in swallowing ability with age, many elderly patients complain that it is difficult for them to take some currently used dosage forms such as tablets, capsules or powders[1]. For this reason, various pharmaceutical dosages which can improve patient compliance have been actively developed. Among them, orally disintegrating tablet is one of the most promising dosage forms. ODTs are the solid unit dosage forms/entities containing medicinal substances which disintegrate or dissolve rapidly in oral cavity usually within a few seconds even without the need of water or chewing[2]. This dosage form also offers an advantage of convenience of administration while traveling where there may not be an easy access to water and combines the advantages of both liquid and tablet formulation[3,4]. Consequently, the pharmaceutical industries as well as academia are taking interest in the development of ODTs by various methods.

Commercially available ODTs are prepared by various techniques mainly direct compression, lyophilisation, moulding, spray drying, sublimation *etc*. Thus, they exhibit different disintegration behavior[5]. The simplicity and cost effectiveness of direct compression process have positioned this technique as an attractive alternate to other technologies[6]. Various superdisintegrants like Ac-Di-Sol (croscarmellose sodium), crospovidone, sodium starch glycolate (explotab) *etc*. have been used in the formulation of ODTs. Various natural sources like *Ocimum basilicum, Ocimum americannum, Plantago ovata, Mimosa pudica*, modified starch and agar can also be used for their disintegrating properties in the formulation of ODTs. Mucilage and gums isolated from these natural sources have been known since ancient times for their medicinal uses. In the modern era also, they are being widely utilized in the pharmaceutical industries as thickeners, water retention agents, emulsion stabilizers, suspending agents, binders and film formers[7,8]. Because of easy availability, comparatively cheaper, non irritating and non toxic nature, substances of natural origin are preferred over synthetic and semi-synthetic ones.

Vomiting or emesis is a protective reflex which leads to expulsion of harmful substances from the upper gastrointestinal tract. The process appears to be coordinated by active participation of vomiting centre present in medulla oblongata through chemoreceptor zone (CTZ) and nucleus tractus solitarius (NTS). Metoclopramide hydrochloride (an antiemetic agent) has central antidopaminergic action on CTZ. At high concentrations, the drug can block $5HT_3$ receptors present on inhibitory interneurons in NTS/CTZ. It has short biological half life and is usually administered in a dose of 10-15 mg, four times a day to maintain effective concentration throughout the day[9].

Plantago ovata Linn. (Family: Plantaginaceae) is a stemless or short stemmed (10-45 cm tall) hairy annual

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Table 1: Composition of Metoclopramide Hydrochloride ODTs.

Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	10	10	10	10	10	10	10	10
Croscarmellose sodium	3.75	7.5	11.25	15	-	-	-	-
Plantago ovata mucilage powder	-	-	-	-	3.75	7.5	11.25	15
Mannitol	116.45	112.70	108.95	105.20	116.45	112.70	108.95	105.20
Microcrystalline cellulose	15	15	15	15	15	15	15	15
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3	3
Sodium saccharin	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

herb. Seeds of *Plantago ovata* are dull, pinkish grey brown, long to elliptical, boat shaped. It is a natural substance having disintegrating, gel forming and binding property[10,11]. The aim of present study was to develop ODTs of selected model drug metoclopramide hydrochloride using croscarmellose sodium as well as mucilage isolated from seeds of *Plantago ovata* and to compare disintegrating property of both.

MATERIALS AND METHODS

Materials

Metoclopramide hydrochloride and microcrystalline cellulose (MCC) were received as a gift sample from Ind Swift Pvt. Ltd., Chandigarh, India. Croscarmellose sodium was generous gift sample from Wockhardt Research Centre, Aurangabad, India. Directly compressible vehicle mannitol (Qualigens Fine Chemicals, Mumbai, India) and magnesium stearate (Loba Chemie, Mumbai, India) were also utilized. *Plantago ovata* seeds were procured from the local market. All other chemicals used were of analytical grade.

Methods

Isolation of Mucilage

For the isolation of mucilage, seeds of *Plantago ovata* were used. They were soaked in distilled water for 48 hours and then boiled for one hour for complete release of mucilage into water. The material was filtered by squeezing in a muslin cloth to remove marc. Then equal volume of acetone was added to filtrate to precipitate the mucilage. The mucilage was separated and dried in an oven at temperature less than 60º C, powdered (80#), weighed and stored in a desiccator until further utilization[12,13].

Formulation of ODTs

ODTs of metoclopramide hydrochloride were prepared by direct compression technique using croscarmellose sodium and mucilage isolated from *Plantago ovata* at concentration of 2.5, 5, 7.5 and 10%. The composition of each formulation is given in Table **1**.

All ingredients were passed through mesh number 60. Required quantity of each was taken for particular formulation and blend was mixed by tumbling in a poly bag for about 5 minutes to achieve complete mixing. Obtained blend was lubricated with magnesium stearate along with the addition of talc and mixed for another 2 minutes[14]. The resultant mixture was directly compressed into tablets using mini rotary tablet machine (Fluid Pack Machinery, Ahmedabad, India) with punches of 7.4 mm. A minimum of 50 tablets were prepared for each batch. Prior to compression into tablets, the blend was evaluated for various parameters such as angle of repose, compressibility index, bulk density, tapped density and Hausner's ratio.

Flow Properties of Blend

There are many formulation and process variables involved in mixing step and all these can affect the characteristics of blend produced. These blends were evaluated (before compression) in terms of bulk density, tapped density, Hausner's ratio, compressibility index and flow properties (angle of repose). For determination of angle of repose (θ), the blend was poured through the funnel until the apex of conical pile touched the tip of the funnel. The $\tan^{-1}$ of the (height of the pile/radius of its base) gave the angle of repose[2].

Bulk density, Tapped density, Hausner's ratio (HR) and Carr's index (CI) were calculated using tap density apparatus. The cylinder was raised and dropped under its own weight by a fixed drop height of 3 mm ± 10% at a nominal rate of 250 drops per minute using tap density apparatus (Electrolab, USP, ETD-1020, Mumbai).

Evaluation of ODTs

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. Hardness was measured using Pfizer type hardness tester[15]. Friability of the tablets was determined in Roche friabilator[16]. Thickness of tablets was measured using Vernier caliper[17]. For drug content uniformity test, one tablet was powdered, selected randomly from each batch and mixed it in 50 ml of 0.1 N HCl. The obtained solution was heated at 70º C for 15 minutes, cooled and diluted to 100.0 ml with water and filtered. To 20 ml of this solution, 15 ml of 1.25 M sodium hydroxide was added and extracted with three quantities, each of 30 ml of chloroform. Each extract was dried with anhydrous sodium sulphate and filtered. The combined extract was diluted to 100 ml with chloroform and mixed. The absorbance of the resulting solution was measured and concentration of metoclopramide hydrochloride was calculated[18]. Wetting time and water absorption ratio were also determined. For these parameters, a piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A

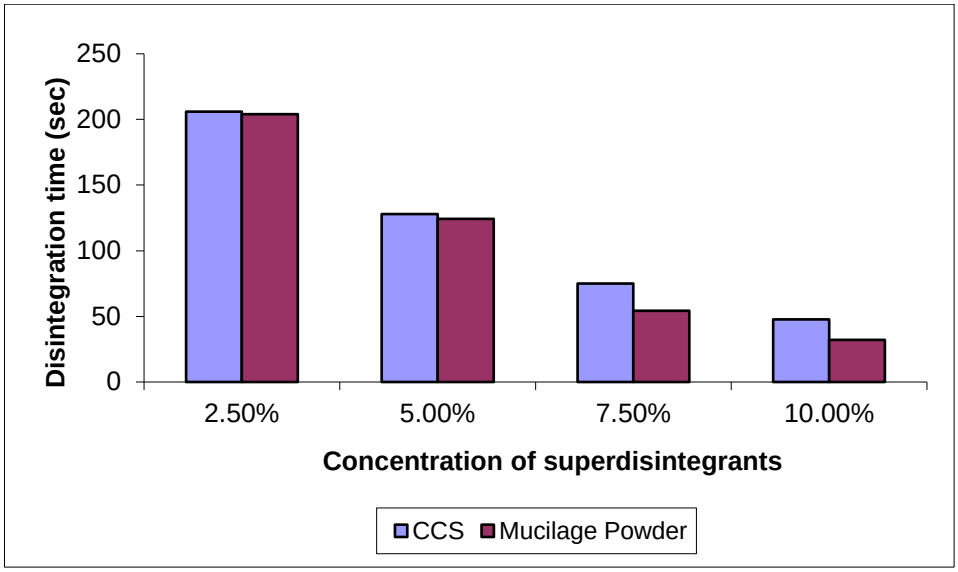

Figure 1: Graphical representation depicting *in-vitro* disintegration time of ODTs.

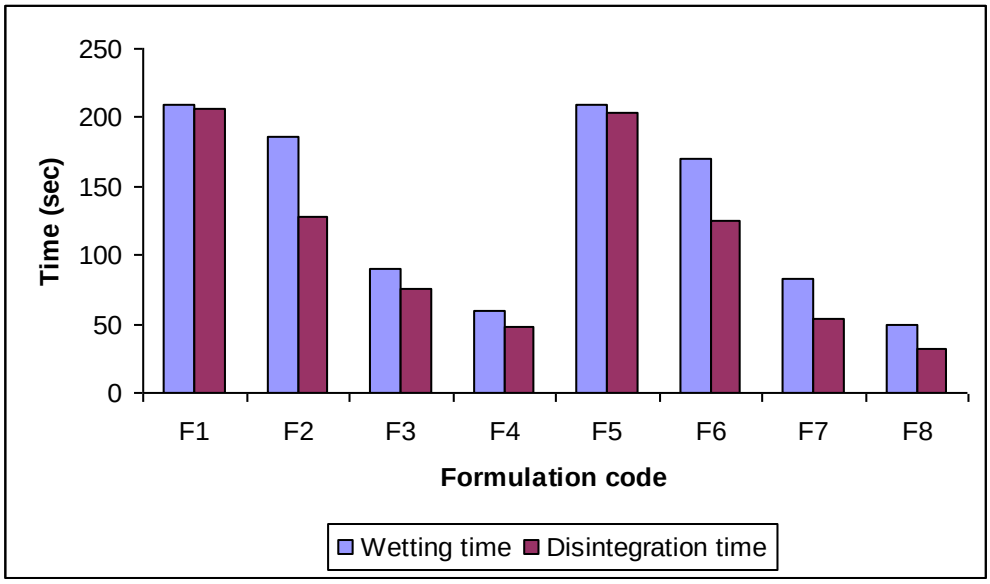

Figure 2: Correlation between disintegration time and wetting time.

tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was weighed. Water absorption ratio was determined using the equation:

$R = 100\times (w_a - w_b) / w_b$

Where w_b and w_a were tablet weights before and after water absorption, respectively[19,20]. Disintegration time was determined using USP disintegration test apparatus without disk for six tablets. Distilled water at 37 ± 0.5 ºC was used as disintegration medium and stirred at a rate of 30 ± 2 cycles/min. The time was measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus[21,22]. *In vitro* drug release of metoclopramide hydrochloride from ODTs was carried out using USP dissolution apparatus type II (paddle type) at 50 rpm in 900 ml of distilled water as dissolution medium maintained at 37 ± 0.5 ºC. Aliquots of dissolution medium (10 ml) were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 309 nm for metoclopramide hydrochloride using double beam UV spectrophotometer. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The dissolution studies were carried out in triplicate for each formulation batch[2,23]. Cumulative percentage drug release was calculated using an equation obtained from standard calibration curve. Standard calibration curve of metoclopramide hydrochloride was prepared using various dilutions of its stock solutions in distilled water. Absorbance was measured for each solution at λ_{max} 309 nm using double beam UV visible spectrophotometer (Systronics, model-2202, Ahmedabad). Results of all evaluating parameters were expressed as mean ± S.D. (n=3).

Swelling Index Studies

The swelling index is the volume in ml taken by one gm of superdisintegrant, or any adhering mucilage after getting

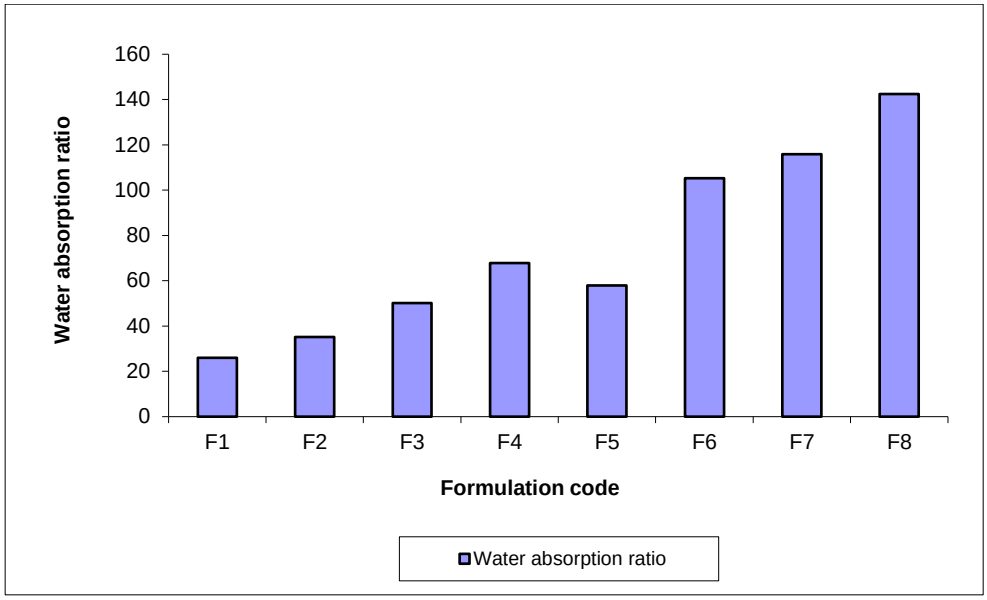

Figure 3: Water absorption ratio of various prepared ODTs.

Table 2: Swelling index of different excipients.

Name of excipient	Swelling index (% v/v)
Plantago ovata mucilage powder	94 ± 2.5
Croscarmellose sodium	85 ± 1.5

swollen in an aqueous liquid for four hours. Swelling index of *Plantago ovata* and croscarmellose sodium was evaluated employing British Pharmacopoeia method. The swelling index was calculated from the mean of three determinations[12,23,24].

Mechanism of Drug Release

To analyze the *in vitro* release data, various kinetics models were used to describe the release kinetics. The suitability of several equations pertaining to different models *i.e.* zero order kinetics, first order kinetics, Higuchi model and Korsmeyer–Peppas model to identify the mechanism for the release of metoclopramide hydrochloride was tested with respect to release data[25-29].

RESULTS AND DISCUSSION

Eight formulations were prepared using different concentration of superdisintegrants under similar conditions to avoid processing variables. Flow properties of the powder can be judged from the angle of repose. The angle of repose < 30º indicates free flowing material and >40º with poor flow properties. Values for angle of repose were found in the range of 25.1º-29.9º depicting that the blend of all designed formulations were free flowing and can be used for direct compression. Bulk density of all prepared formulations was found in the range of 0.472-0.522 g/cm^3 and tapped density was between 0.607-0.670 g/cm^3. Compressibility index of all prepared formulations was found to lie in the range of 20.43 to 25.67% revealing fair to good flow properties. Hausner's ratio is related to interparticle friction. Powders with low interparticle friction have ratio of approximately 1.2, whereas more cohesive, less free flowing powders have ratio >1.6. Hausner's ratio for all prepared formulations was between 1.26-1.35 indicating low interparticle friction. No prepared formulations revealed Hausner's ratio >1.6. As the material was free flowing, tablets obtained were of uniform weight due to uniform die fill, with acceptable variations as per I.P. 1996 specifications *i.e.* below 7.5%. Drug content of all formulations was found to be between 96.3-100.01% which is within acceptable limits. Hardness was found to be in the range of 3.0-3.5 kg/cm^2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling.

The percentage friability was ranged from 0.40-0.80% for all the designed formulations which is within limit *i.e.* is less than 1.0% except for F8 (1.3%) which inferred that mucilage powder has strong binding capacity at concentration of 2.5-7.5%, beyond this concentration the binding efficiency decreases. *In vitro* disintegration time of various formulations was also calculated using disintegration test apparatus. After observing the disintegration time, it was concluded that as the concentration of the superdisintegrant increases, the disintegration time decreases. It has been represented in Figure **1** by plotting a bar graph between disintegration time and different concentration of superdisintegrants. Wetting time was used as parameter to correlate with disintegration time. Disintegration time was found to be in between 32 to 206 seconds for all the formulations and wetting time was reported in between 50 to 209.7 seconds for all the prepared formulations. This showed good correlation between disintegration time and wetting time. It was revealed that lesser the wetting time, shorter would be the disintegration time. A correlation between wetting time and disintegration time has been shown in Figure **2**. Wetting time results are in consistent with the findings of disintegration test.

Water absorption ratio is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water. Water absorption ratio of the tablets from all formulation batches was calculated

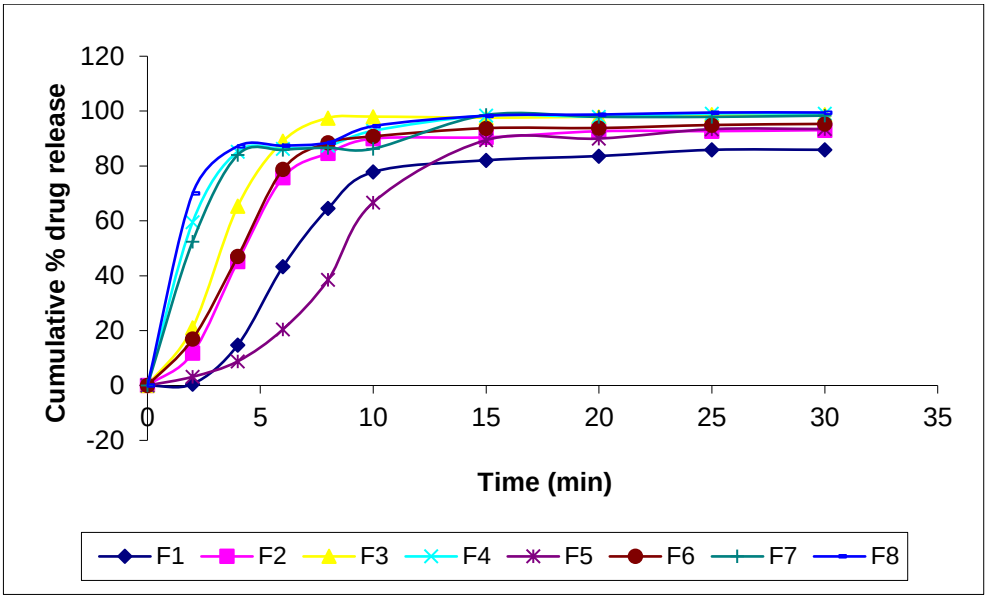

Figure 4: Dissolution profile of various formulations containing mucilage powder and croscarmellose sodium.

according to procedure and formula as illustrated earlier. It was within the range of 26.02-142.54. The water absorption ratio of mucilage powder was higher as compared to that of croscarmellose sodium. It was observed that water absorption ratio increased with an increase in superdisintegrant concentration ranging from 2.5-10.0%. Observations are represented in Figure **3**.

Swelling index of both disintegrants has been given in Table **2**. Because of higher swelling index the formulations containing *Plantago ovata* mucilage powder disintegrated quickly and completely. Rapid disintegration of ODTs was due to the penetration of saliva into the pores of tablets which leads to swelling of superdisintegrant to create enough hydrodynamic pressure for quick and complete disintegration of the tablets. Croscarmellose sodium works by swelling and wicking action. *In vitro* drug release studies for all the developed formulations were carried out in triplicate manner. It is evident that disintegration has effect on the dissolution characteristics and an increase in superdisintegrant concentration resulted in increasing order of cumulative percentage drug release in the first 4 minutes. This may be attributable to the increase in concentration of superdisintegrant which resulted in rapid disintegration of tablets and the particles were exposed to dissolution medium at a comparatively faster rate. Percent drug released at various intervals from 2-30 minutes was determined by using equation obtained from calibration curve. F1, F2, F3 and F4 formulations with croscarmellose sodium were found to release 14.75%, 45.20%, 65.36% and 85.24% of drug respectively in the first four minutes. Likewise, formulations F5-F8 released 8.81%, 47.05%, 84.05% and 87.23% of drug respectively at the end of 4 minutes. The plot between cumulative percentage drug release versus time as portrayed in Figure **4** revealed that the formulations F3, F4, F7 and F8 released more than 95% of drug at the end of 15 minutes. Drug release rate from the formulations with mucilage powder was also found to be fast as compared to the formulations containing croscarmellose sodium. Rapid increase in the dissolution of metoclopramide hydrochloride with increase in mucilage powder may be attributed to swelling of mucilage powder on penetration of water into the pores of tablets and generation of hydrodynamic pressure for quick and complete disintegration of tablets.

The release data of all the formulations were fitted into four different mathematical models specifically zero order, first order, Higuchi model and Korsmeyer-Peppas (power law) model to characterize the mechanism of drug release. The release rate constants (K_0, K_1, K_H) and correlation coefficients (R^2) as obtained from regression plots of different kinetic models such as zero order, first order, Higuchi and the release exponent value (n) for power law of all the formulated orally disintegrating tablets have been described. Considering the correlation coefficient (R^2) values as obtained from the different kinetic equations, the drug release from most of the formulated ODTs were found to follow first order model rather than other models. The first order kinetic describes the system where the drug release rate is dependent on its concentration. Correlation coefficient (R^2) value obtained in zero order, first order, Higuchi and Peppas release kinetic of formulation F1 were 0.704, 0.790, 0.782 and 0.702 respectively. In this formulation, *in vitro* drug release was best explained by first order because best linearity was found in first order equation plot (R^2 = 0.790) as indicated by their highest correlation coefficient value as compared with other models. On considering the R^2 value for F5, the drug release was best explained by Korsmeyer-Peppas model, as the plot showed the highest linearity (R^2 = 0.909), but a close relationship was also noted with first order kinetics (R^2 = 0.907). The value of release exponent (n) obtained from Korsmeyer-Peppas model gives an indication of the drug release mechanism. The release exponent "n" value for the different formulation ranged from 0.12-1.55.

However, the formulations F2 and F6 showed the diffusional exponent; "n" in between 0.5 and 1.0 which

indicates the anomalous transport kinetics or non-fickian diffusion that means the drug was released by the combined mechanism of pure diffusion controlled and swelling controlled drug release. For the formulation F3 "n" is approximately 0.5 (*i.e.* 0.45) indicates that drug was released by pure diffusion controlled mechanism (Fickian diffusion). The formulations F1 and F5 having "n" value greater than 1 were found to follow supercase II transport. The remaining formulations (F4 and F7-F8) having "n" value less than 0.5 were beyond the limits of Korsmeyer-Peppas model.

CONCLUSION

The present investigation revealed that natural superdisintegrant such as *Plantago ovata* mucilage powder showed better and promising disintegrating profile than the synthetic superdisintegrant like croscarmellose sodium. ODTs prepared by using natural superdisintegrant disintegrated quickly. This might be attributable to higher swelling of *Plantago ovata* mucilage powder as compared to formulations containing croscarmellose sodium. Because mucilage powder is inexpensive, nontoxic, compatible and easy to manufacture as compared to synthetic superdisintegrant, it can be employed as a potential candidate for use as a natural superdisintegrant in the development of ODTs. Significant findings of the present work may be utilized by scientific community for development of superior dosage forms in the near future.

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