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Formulation Strategies for Orally Disintegrating Tablets of Diclofenac Sodium Employing Natural Pectin Derived from Malus domestica

Kondapuram Parameshwar[1], Ch.Srinivas Reddy[2], Shaik harun rasheed[3], Marla Rajendar[4], Ramachakradhar Devani[5], I. Rajendra Prasad[6], Ashok Velpula[7]

[1-4] Gurunanak Institutions Technical campus, School of Pharmacy, Hyderabad, Telangana, 501506, India.

[5-7] Gitam School of Pharmacy, Gitam deemed to be University, Visakhapatnam530045, India

*Corresponding Author: Dr.K. Parameshwar: Email- parameshwarkp@gmail.com

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ABSTRACT

This study aimed to develop and evaluate diclofenac sodium orally disintegrating tablets (ODTs) using Malus domestica (apple) as a natural pectin source, which may also possess anti-inflammatory properties. Diclofenac sodium ODTs were formulated utilizing different concentrations of Malus domestica pectin as a disintegrant and binder. The tablets were assessed for their physicochemical properties, including hardness, friability, weight variation, and disintegration time. The in vitro release profile of diclofenac sodium from the ODTs was examined using a USP dissolution apparatus. The formulated ODTs demonstrated satisfactory physicochemical properties, with appropriate hardness, minimal friability, and rapid disintegration times. The in vitro release studies revealed a swift release of diclofenac sodium, with over 90% of the drug released within the limit. Furthermore, the ODTs containing higher concentrations of Malus domestica. Pectin showed enhanced anti-inflammatory activity the study successfully developed diclofenac sodium ODTs using Malus domestica. as a natural pectin source. The tablets exhibited promising physicochemical properties, rapid drug release, and improved anti-inflammatory activity. These findings suggest that Malus domestica pectin can serve as an effective excipient in the formulation of ODTs, offering potential therapeutic benefits.

Keywords: Orally disintegrating tablets, Malus domestica, Natural pectin, Anti-inflammatory activity.

INTRODUCTION

Orally disintegrating tablets (ODTs) have become increasingly popular in the pharmaceutical field due to their ability to quickly disintegrate in the mouth, providing a convenient dosing option that does not require water. This characteristic makes ODTs particularly suitable for pediatric, geriatric, and dysphagic patients, enhancing patient compliance and convenience. The formulation of ODTs involves the use of superdisintegrants, which are critical in achieving swift disintegration and ensuring rapid drug release. Diclofenac sodium is a commonly prescribed non-steroidal anti-inflammatory drug (NSAID) used to manage pain and inflammation associated with a variety of conditions, including arthritis, menstrual pain, and migraines. The development of diclofenac sodium ODTs represents an opportunity to provide patients with a fast-acting and convenient form of this medication, potentially improving therapeutic outcomes [1, 2].

Recent trends in pharmaceutical formulation have seen a shift towards the use of natural polymers as excipients, driven by their biocompatibility, biodegradability, and general recognition as safe (GRAS) materials. Apple pectin commonly known as the Malus domestica tree, is a rich source of natural pectin. Pectin is a polysaccharide that has found applications as a gelling agent, stabilizer, and disintegrant in both the food and pharmaceutical industries. Interestingly, pectin from Malus domestica. Has also been reported to exhibit anti-inflammatory properties, which could complement the therapeutic effects of diclofenac sodium [3].

In this study, we aim to formulate and evaluate diclofenac sodium (Figure 1) ODTs using Malus domestica. As a natural source of pectin. The investigation encompasses the assessment of the physicochemical properties of the tablets, their disintegration behavior, drug release profile, and potential anti-inflammatory activity. The utilization of Malus domestica Pectin as a disintegrant in ODTs is a novel approach that holds promise for enhancing the functionality and therapeutic efficacy of the dosage form [4].

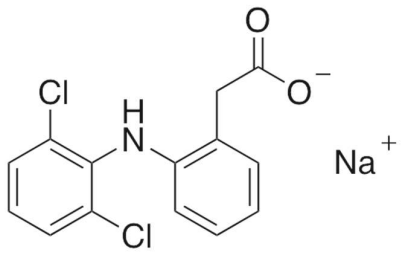

Figure 1: Chemical Structure of Diclofenac Sodium

MATERIAL AND METHODS

Material

Fresh apples (Malus domestica) was acquired from Hyderabad, India, while diclofenac sodium was sourced from SD Fine Pvt. Ltd. in Mumbai. Microcrystalline cellulose and SSG were obtained from SD Fine Chemicals, and Crosscarmellose sodium was procured from Arrow Chem. Product, Mumbai. All

ingredients used in the study were of analytical grade.

Extraction of Pectin Powder from Malus domestica (Apple)

Begin by selecting fresh apples. Peel the apples to obtain the peels, which will be used for extraction. Measure 10 grams of dried apple peel powder using an analytical balance. Mix the dried apple peel powder with 100 mL of distilled water in a suitable container. Acidify the mixture. Stir the mixture with a mechanical stirrer for 120 minutes to ensure uniform wetting of the powder by the acidified water, resulting in a homogeneous mixture. Treat the acidified mixture with 90% ethanol. Allow the mixture to stand at room temperature for 12 hours to facilitate pectin precipitation. After 12 hours, recover the precipitated pectin by filtration. Mix the collected pectin with double the volume of 95% ethanol to enhance precipitation. Store the samples in a dark environment at room temperature for 24 hours to promote pectin flotation. Separate the floated pectin by filtration and wash it twice with 70% ethanol to remove impurities. Add acetone drop wise to the pectin mixture to eliminate any unwanted color. Place the purified pectin substance in a vacuum desiccator until a constant weight is reached. Once dried, grind the pectin into a fine powder using a mortar and pestle or a grinder. Determine the percentage yield of the extracted fruit pectin by calculating the grams of product obtained per gram of dried apple peel powder used. [5, 6].

Preparation of diclofenac sodium ODTs

The pectin used in this study was prepared by extracting it from Malus domestica fruit pulp. The drug, diluents, and binders were all precisely weighed and then passed through a 40-mesh screen. To form a wet dough mass, the required amount of water was added. Wet granules were then produced by passing the wet mass through a 22-mesh screen. The granules were dried in an oven at 70°C. Once dried, they were passed through a 44-mesh sieve and subsequently blended with magnesium stearate and talc. The resulting granular mixture was then compressed into tablets using an 8-station rotary tablet machine equipped with a 3mm round flat-faced punch. The compression force was maintained constant for all formulations. **Table 1** details the composition of diclofenac sodium orally disintegrating tablets (ODTs) incorporating Malus domestica fruit pectin, both with and without mannitol, prepared using the wet granulation method [7].

Table 1: Formulation of diclofenac sodium Oral disintegrating tablets (n=3)

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Diclofenac sodium	50	50	50	50	50	50	50
Microcrystalline Cellulose	6	6	6	6	6	6	6
Malus domestica powder	5	7.5	10	5	7.5	10	-
Lactose	114	111.5	109	130	135	140	119
Mannitol	50	50	50	-	-	-	50
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of tablets

All the tablets were assessed for various physical parameters, including weight variation, hardness, friability, disintegration time, wetting time, drug content, and in vitro dissolution study [8,9]

Weight variation

The weight variation test is conducted to verify the uniformity in the weight of tablets within a batch. This is achieved by first determining the total weight of 20 tablets from each formulation and then calculating the average weight. Subsequently, the individual weight of each tablet is determined to assess the weight variation.

$$\%\,\text{Weight variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100 \text{ (Equation 3)}$$

Hardness

Hardness of tablets was measured using Pfizer type hardness tester. Three tablets were selected from each formulation randomly and their hardness was measured. The mean± SD of hardness values were calculated.

Friability test

Friability is defined as the loss of weight of a tablet in the container due to the removal of fine particles from its surface. The friability test is conducted to assess the tablet's ability to withstand abrasion during packaging, handling, and transportation. The Roche friabilator is used to determine the friability of the tablets. In this test, 20 tablets from each batch are weighed and placed in the Roche friabilator, which rotates at 25 rpm for 4 minutes. After the test, the tablets are dedusted and reweighed. The percentage of friability can be calculated using the formula:

$$\% \text{ Friability} = [\frac{W1-W2}{W1}] \text{x}100 \text{ (Equation 4)}$$

Wetting time

The wetting time of the tablets is measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petri dish containing 3 ml of a 0.2% w/v solution. A tablet is carefully placed on the surface of the tissue paper. The time required for the blue color to develop on the upper surface of the tablet is noted as the wetting time

***In -Vitro* disintegration test**

The in-vitro disintegration time is determined by placing a tablet in a beaker containing 50 ml of buffer pH 6.8. Three tablets from each formulation are randomly selected, and the in-vitro dispersion time is then conducted.

***In-Vitro* dissolution test**

The dissolution rate of diclofenac sodium tablets was investigated in 900 ml of phosphate buffer at pH 6.8 using an Electro lab (TDT-082) 8-station dissolution test apparatus equipped with a paddle stirrer operating at 50 rpm. The temperature was maintained at 37±0.5°C throughout the study. Samples of the dissolution media (5 ml) were withdrawn at various time intervals, suitably diluted, and assayed at 276 nm. The withdrawn samples were replaced with fresh dissolution fluid. Each dissolution experiment was conducted in triplicate (n=3).

Accelerated Stability Testing

The stability of diclofenac sodium oral disintegrating tablets in different formulations was studied at two storage conditions. One sample is kept at room temperature 40 ± 2°C and 75 ± 5% Relative Humidity (RH) for three months. The samples analyzed for tablets physical stability.

RESULTS

The physicochemical characterization of the extracted Malus domestica fruit Pectin was evaluated. The Loss on drying of the Malus domestica fruit Pectin were found to be 7.2±0.15%, respectively. The pH was observed to be within the specified limit. In terms of micrometric studies, the Swelling Index was determined to be 2.0 and the tapped density was 0.65 g/cm3. From the Viscosity to be 300 m Pa•s The angle of repose was found to be 22.4°, and Hausner's ratio indicating that the pectin falls within acceptable limits

Table 2: Physical evaluation of ODTs diclofenac sodium

Sr. No	Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegrating Time (sec)	Wetting time (sec)	*In-Vitro* dissolution
1	F1	199.6±0.21	3.2±0.02	0.6±0.1	14±1.22	24±0.41	95.25±0.422
2	F2	198.7±0.25	3.0±0.01	0.5±0.4	11±1.43	22±1.17	97.18±0.419
3	F3	196.4±0.21	3.1±0.02	0.4±0.2	13±1.37	23±2.41	98.42±0.422
4	F4	199.4±0.27	3.3±0.02	0.7±0.1	19±1.24	35±2.54	93.67±0.413
5	F5	198.8±0.31	3.2±0.01	0.6±0.3	18±1.22	33±3.49	94.45±0.422
6	F6	199.1±0.26	3.2±0.01	0.5±0.4	17±2.47	30±1.42	96.95±0.431
7	F7	198.6±0.22	3.5±0.03	0.8±0.2	18±3.47	25±0.39	38.74±0.405

(Mean + SD) (n=3)

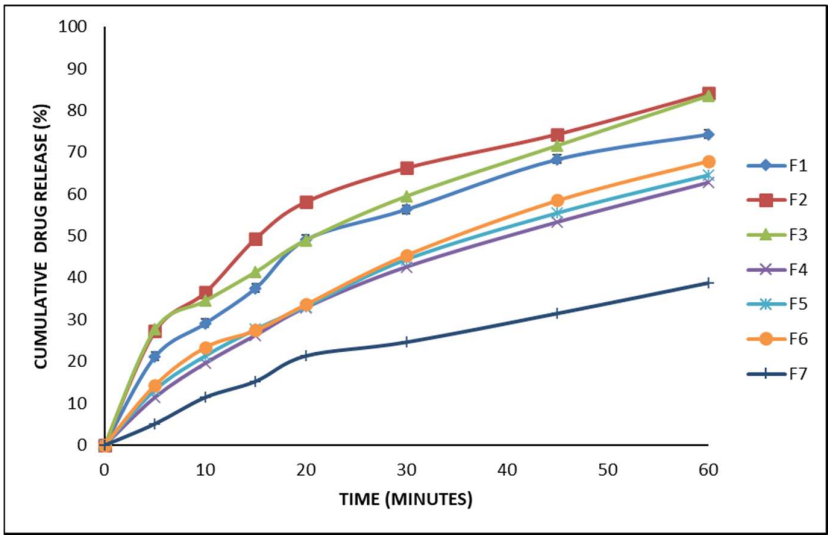

Figure 1: *in vitro* Drug release profile of Diclofenac sodium ODT

Table 2: The data obtained from the study Drug release parameters

Formulation Code	Kinetic parameters											
	Zero order			First order			Higuchi			Korsmeyer-peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
F_1	15.769	1.133	0.938	1.947	0.010	0.987	0.147	10.006	0.995	0.960	0.527	0.993
F_2	21.478	1.211	0.912	1.927	0.012	0.987	3.340	10.965	0.991	1.127	0.460	0.990
F_3	18.013	1.204	0.946	1.954	0.012	0.993	1.323	10.579	0.999	1.099	0.456	0.996
F_4	8.021	0.997	0.975	1.979	0.007	0.997	4.483	8.447	0.993	0.603	0.684	0.997
F_5	8.921	1.017	0.974	1.976	0.007	0.997	3.939	8.641	0.995	0.681	0.643	0.999
F_6	9.136	1.069	0.977	1.980	0.008	0.998	4.202	9.040	0.993	0.720	0.628	0.998
F_7	4.193	0.618	0.975	1.985	0.003	0.988	3.433	5.209	0.987	0.236	0.782	0.985

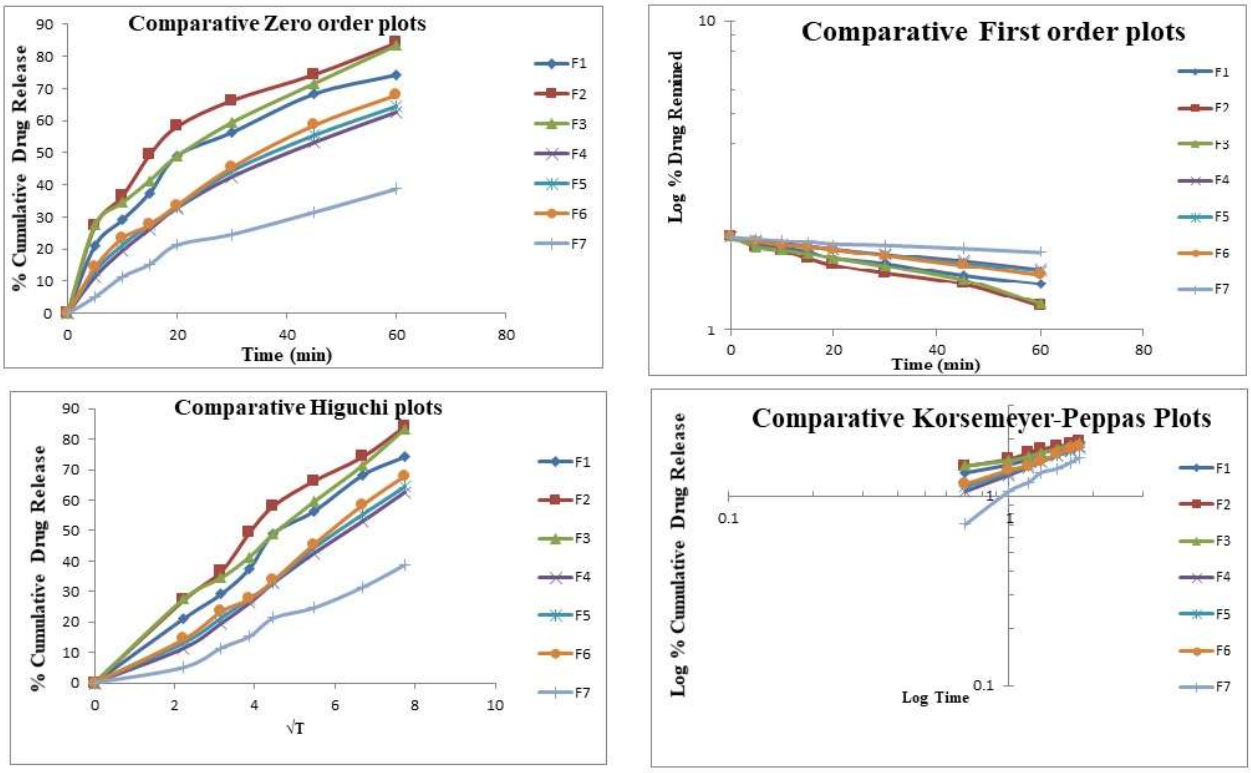

Figure 3: Kinetic parameters of formulation F1-F7 of ODTs of Diclofenac sodium

Table 4: stability studies of optimized formulation F3 baobab pectin co-processed ODT tablets of diclofenac sodium

Code	Initial Weight variation (mg)	2-8˚ C		Room Temperature		40±2 ˚C/ 75% RH	
		Weight variation (mg) after 15 days	Weight variation (mg) after 3 months	Weight variation (mg) after 15 days	Weight variation (mg) after 3 month	Weight variation (mg) after 15 days	Weight variation (mg) after 3 month
F3	199.2±0.21	199.1±0.15	199.1±0.11	199.1±0.23	199.1±0.1	199.1±0.04	198.1±0.01

DISCUSSION

In this study, In this study, we explored the formulation of diclofenac sodium oral disintegrating tablets (ODTs) using Malus domestica fruit Pectin, and the influence of mannitol as a diluent was also examined. The formulations F1 through F7 demonstrated varying degrees of physical robustness, disintegration efficiency, and drug release profiles, which are critical for the practical application of ODTs.The weight variation results for all formulations fell within the pharmacopoeia limit of ±5%, which is essential for ensuring dose uniformity. Formulations F2 and F3 presented the most consistent weight profiles, which indicates a high level of control during the manufacturing process. The hardness of the tablets is a balancing act; while a certain degree of hardness is required for handling, excessive hardness can retard disintegration. Formulations F1 through F6 showed a desirable hardness range of 2.8 to 3.4 kg/cm^2,

whereas F7, with a hardness of 3.5 kg/cm², may be at the upper limit for ODTs, potentially impacting the disintegration time.

Friability below 1% is considered ideal for maintaining the integrity of tablets during packaging, shipping, and handling. Our formulations achieved friability well below this threshold, with F3 showing the lowest value at 0.4%, suggesting a robust tablet with less propensity for degradation upon handling.

Rapid disintegration is a hallmark of an effective ODT. In this aspect, Formulation F3 excelled, with a disintegration time of 18 seconds, well below the often-cited target of 30 seconds or less, which may provide a rapid onset of action, enhancing the patient experience. The wetting time is another crucial factor that indirectly affects the rate of disintegration and subsequent drug release. Our results indicate that all formulations had acceptable wetting times, with Formulation F3 showing the shortest time, which may facilitate faster absorption.

Lastly, the in-vitro dissolution of above 90% within the first 30 minutes for all formulations is indicative of a rapid release profile. Formulation F3 showed the highest dissolution percentage at 98%, which could potentially translate into improved bioavailability. Collectively, these results suggest that the use of Malus domestica fruit Pectin in the formulation of ODTs is promising, providing effective disintegration and dissolution profiles. The absence of mannitol (F7) resulted in a suboptimal disintegration profile, which supports its role in creating a porous matrix that aids in tablet disintegration. Therefore, the inclusion of mannitol in the formulations appears to be beneficial. The present study underscores the intricate balance required between tablet hardness, friability, disintegration, and dissolution characteristics. Formulation F3 emerged as the most promising formulation, indicating that the higher concentration of Malus domestica fruit Pectin, combined with the other excipients, produces a tablet that meets the ideal criteria for an ODT. This formulation presents a potential improvement in patient compliance due to ease of administration, which is especially pertinent for populations with swallowing difficulties. Future studies could focus on the post-administration effects, patient acceptability tests, and long-term stability studies to further validate the clinical applicability of the proposed formulation. Additionally, exploring the cost-effectiveness of Malus domestica fruit Pectin could make this an attractive option for widespread use in ODT formulations.

CONCLUSION

The research undertaken to formulate diclofenac sodium oral disintegrating tablets using Malus domestica fruit Pectin has yielded substantial insights into the design and optimization of ODTs. The study conclusively demonstrates that Malus domestica fruit Pectin is an effective superdisintegrant that confers robust disintegration properties to the tablets. Formulation F3, containing 10 mg of Malus domestica fruit Pectin without Mannitol, has emerged as superior, with its rapid disintegration time of 13 seconds, low friability of 0.4%, and high in-vitro dissolution rate of 98%. This formulation strikes an optimal balance between physical integrity and quick drug release, meeting the critical requirements for ODTs in terms of rapid onset of action and ease of administration without the need for water.

The results underscore the potential of Malus domestica fruit Pectin as a natural and effective excipient that could improve patient compliance, especially among those who have difficulty swallowing tablets. The incorporation of Malus domestica fruit pectin in ODT formulations can be considered a promising strategy for delivering medications in a patient-friendly manner. Future work should aim to extend the current findings through clinical trials to assess the bioavailability, patient satisfaction, and comparative efficacy of the developed formulations. Additionally, long-term stability studies under various storage conditions will be critical to further establish the commercial viability of the proposed ODTs.

The implications of this research are poised to contribute to the fields of pharmacy and drug delivery systems by providing a viable alternative to synthetic superdisintegrants, thus opening the door to more natural, sustainable, and potentially cost-effective pharmaceutical excipients.

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