



Formulation and Evaluation of Sustained Release Tablets Using *Prunus armeniaca* (L.) and *Prunus domestica* (L.) Gums

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Abstract

The plant gums obtained from *Prunus armeniaca* and *Prunus domestica* (Family Rosaceae) were studied for their sustained release potential in comparison with hydroxypropyl methyl cellulose (HPMC), a semi-synthetic matrix polymer, using diclofenac sodium. Matrix tablets of diclofenac sodium were prepared using different ratios of gum alone and in combination (i.e. 1:1) with diclofenac sodium and other excipients. The formulated matrix tablets were evaluated for their thickness, hardness, weight variation, friability, drug content and in vitro release studies. These studies demonstrated that *P. armeniaca* and *P. domestica* gums used alone could not control drug release efficiently, however, extended drug release (up to 10 hours) was obtained when both gums were used in combination (1:1). The dissolution data was fitted into zero order, first order, Higuchi and Korsmeyer equation, which dictated that the release mechanism is diffusion as well as erosion controlled-drug release. FTIR studies showed that there was no interaction between drug and plant gums used. Among various formulated batches, F-5 did not significantly differ from F-7 and commercially available formulation (Voltral SR[®], Novartis Pharma, Pakistan) with respect to drug release.

Keywords: Diclofenac sodium; *Prunus armeniaca* gum, *Prunus domestica* gum, Sustained Release Matrix tablets.

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1. Introduction

Plant derived natural polysaccharides are

more suitable pharmaceutical excipients due to non or low toxicity, stability, availability, renewability and are, therefore, extensively used as matrix formers in modified release dosage forms [1, 2]. Natural gums obtained from plants have various applications in drug

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delivery as disintegrant, emulsifying agent, suspending agents, binders and are also useful in formulating immediate and sustained release preparations [3-5].

Prunus armeniaca (L.) and *Prunus domestica* (L.) belong to Rosaceae family, are small to medium size trees, found throughout Pakistan including Azad Jammu and Kashmir region [6].

Prunus armeniaca (L.) commonly called Apricot is used as an antidote, an expectorant, a tonic and an anthelmintic. It is used in traditional medicines for the treatment of fever, cold, cough, asthma, bronchitis, laryngitis, constipation, anemia, hemorrhages and certain tumors. It is also believed to increase fertility. A decoction of the plant bark has been reported as an astringent to soothe irritated skin [7]. *Prunus domestica* (L.) fruits are used locally to treat jaundice and hepatitis and its gum is used as a tonic, laxative, and vermifuge [8, 9]. Hydroxypropylmethyl cellulose (HPMC), a widely used synthetic polymer in sustained release formulation and was, therefore, used for comparison with natural gums i.e. *P. armeniaca* and *P. domestica* gums [10].

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID), which is poorly soluble in water and freely soluble in organic solvent like methanol. It is commonly used as analgesic, antipyretic, anti-inflammatory and for the long-term treatment of rheumatoid

arthritis [11]. Due to its short biological half of 1-2 hours, multiple dosing is required for maintenance of blood therapeutic drug level. Long-term administration of diclofenac sodium, however, leads to side effects including gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding [12, 13].

In order to increase patient compliance and reduce the incidence of adverse effects, the aim of current study was to prepare sustained release formulation using natural gums of *P. armeniaca* and *P. domestica* alone and in combination in comparison to commercially available standard formulation.

2. Materials and methods

2.1. Materials

Diclofenac sodium, Avicel pH 101, Aerosil, magnesium stearate, and HPMC (Methocel K₁₀₀) were a kind gift of Prays Pharmaceuticals (Pvt) Ltd, Islamabad, Pakistan. Hydrochloric acid, methanol, sodium hydroxide and potassium dihydrogen phosphate were purchased from Musaji and Sons, Khyber Bazaar, Peshawar, Pakistan. All other chemicals used were of analytical grade.

2.2. Methods

2.2.1. Collection of *Prunus armeniaca* and *Prunus domestica* gums

Gums were collected from the plants of *P. armeniaca* and *P. domestica*, (Family Rosaceae) in April, 2010 from Sheringal

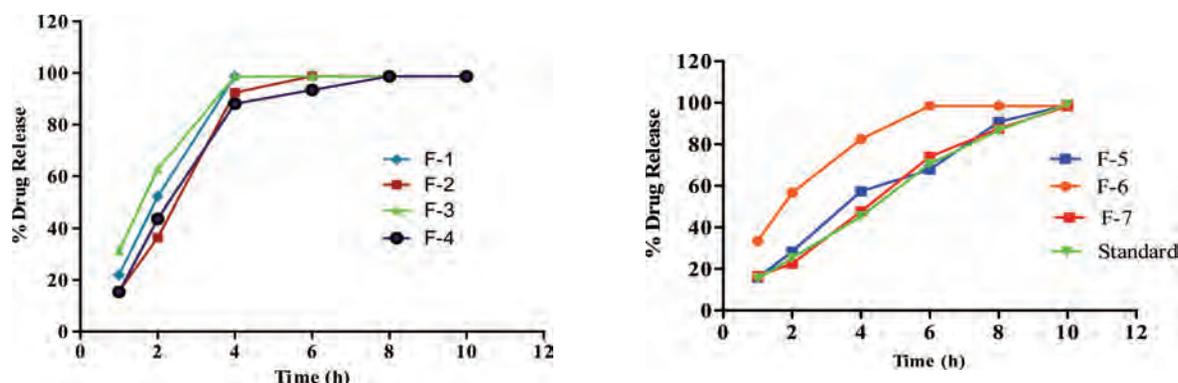


Figure 1. In vitro dissolution profile of formulations of F-1 to F-4 (a) and F-5 to F-7 and Standard (b).

Table 1. Formulation batches of diclofenac sodium matrix tablets containing PAG (*Prunus armeniaca gum*) and PDG (*Prunus domestica gum*).

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Diclofenac sodium	50	50	50	50	50	50	50
Avicel pH 101	93	43	93	43	43	93	43
PAG	50	100	-	-	50	-	-
PDG	-	-	50	100	50	-	-
HPMC	-	-	-	-	-	50	100
Distilled water	q.s						
Aerosil	4	4	4	4	4	4	4
Magnesium stearate	3	3	3	3	3	3	3
Total weight	200	200	200	200	200	200	200

Key: - = absent; q.s = quantity sufficient

valley of District Dir Upper, Khyber Pakhtunkhwa, Pakistan. Both gums were natural exudates on the bark of the plants. The plants were identified by Prof. Dr. Jehandar Shah, Vice Chancellor, Shaheed Benazir Bhutto University, Sheringal (Dir Upper) Khyber Pakhtunkhwa, Pakistan. The specimen samples (PG-01-10 and PG-02-10) were kept in Department of Pharmacy, University of Malakand, Chakdara, Dir Lower, Khyber Pakhtunkhwa, Pakistan. After collection, both gums were dried in oven at 60 °C. Gums were then solubilized in distilled water to remove extraneous materials by straining through a muslin cloth. The gums were then precipitated from the solution using absolute acetone. The precipitate was separated, dried in oven at 50 °C and stored in tightly closed container for future use in formulating sustained release matrix tablets.

2.3. Pre-formulation studies

Calibration curve for diclofenac sodium: calibration curve of diclofenac sodium was constructed by dissolving diclofenac sodium (50 mg) in 50 ml phosphate buffer (pH 7.4) to prepare stock solution (1 mg/ml). Dilutions (5, 10, 15 and 20 µg/ml) were prepared from stock solution. By scanning one of the dilutions in the range of 400 to 200 nm using a double beam UV- visible spectrophotometer (UV-1601 Shimadzu, Japan), λ_{\max} of the drug was determined [11].

2.4. Preparation of granules

Granules of various formulations containing 50 mg of diclofenac sodium were prepared by wet granulation method. Natural gums alone (*P. armeniaca* and *P. domestica gums*) with a drug: gum ratio of 1:1 and 1:2 and HPMC in ratio of both 1:1 and 1:2 were used as standard release retardant. Total weight of tablet was kept as 200 mg. Diclofenac sodium, Avicel pH 101, Aerosil and gums (*P. armeniaca* and *P. domestica gums*) were separately mixed, thoroughly, and sufficient quantity of water was added as granulating agent. The damp mass was passed through mesh 12. Granules obtained were allowed to dry at 60 °C for 4-5 h and were then passed through mesh 18. Finally magnesium stearate was added as lubricant to each batch, as shown in Table 1.

2.5. Evaluation of granules

The bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose were determined for each batch of dried granules.

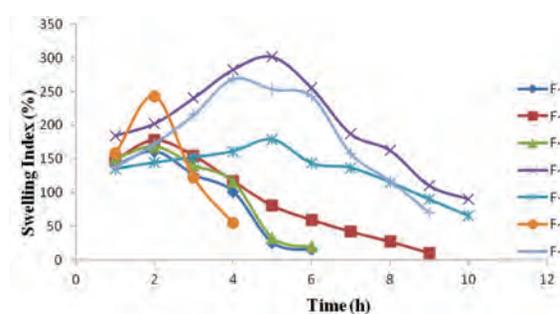


Figure 2. Swelling index of batches F-1 to F-7.

Table 2. Properties of the granules.

Tablets batches	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Hausner's ratio	Angle of repose (°)
F-1	0.58±0.01	0.66±0.01	11.66±0.60	1.12±0.00	29.11±2.21
F-2	0.60±0.01	0.68±0.01	11.99±0.01	1.13±0.00	32.43±1.03
F-3	0.56±0.01	0.64±0.03	11.99±0.51	1.13±0.01	30.37±2.90
F-4	0.54±0.07	0.61±0.01	10.00±0.13	1.12±0.01	36.49±0.65
F-5	0.62±0.00	0.74±0.01	17.26±1.56	1.20±0.03	32.41±0.41
F-6	0.57±0.00	0.70±0.01	19.65±0.59	1.24±0.00	36.86±0.94
F-7	0.47±0.00	0.56±0.00	15.82±1.25	1.18±0.02	33.50±1.17

• All values represents means±SD; n=3.

2.5.1. Bulk density

Granules of known weight (m) were poured in 10 ml graduated cylinder, unsettled volume (V₀) was noted and bulk density was calculated (g/ml) by formula m/V₀ [14].

2.5.2. Tapped density

The graduated cylinder (10 ml) containing known weight (m) of granules was tapped on a hard surface until no further change in volume was observed. The tapped volume (V_T) was noted and tapped density was calculated by putting values in formula, m/ V_T [15].

2.5.3. Compressibility index

It was determined by Carr's compressibility index i.e.

$$\text{Compressibility index} = (T_d - B_d / T_d) \times 100$$

Where T_d is tapped density and B_d is bulk density.

2.5.4. Hausner's ratio

It was calculated by the formula [16]:

$$\text{Hausner's ratio} = T_d / B_d$$

Where T_d is tapped and B_d is bulk density.

2.5.5. Angle of repose

It was determined by filling powder (10 g) in a funnel. Then, the funnel was opened to release the powder on the paper to form a conical heap. The values were calculated by formula [16],

$$\tan \theta = h/r \text{ or } \theta = \tan^{-1} h/r$$

Where h = height of the heap, and r = radius of the heap.

2.6. Preparation of sustained release matrix tablets

Tablets were prepared by compressing granules on rotary compression machine using shallow concave die (8 mm) and punch set (ZP19 Rotary Tablet Press, Shanghai, China).

2.7. Evaluation of compressed tablets

2.7.1. Average weight

Twenty tablets were selected randomly and weighed individually by analytical balance (Sartorius BL 2105, Germany) after compression, calculated average weight and

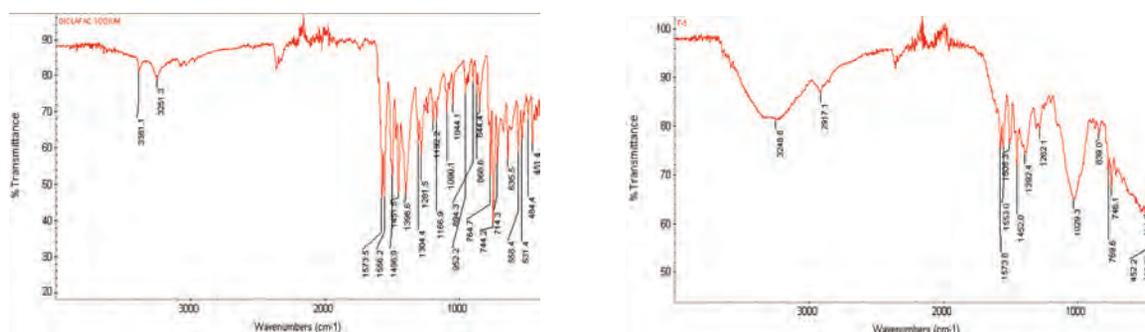


Figure 3. FT-IR of (a) pure diclofenac sodium, and (b) formulation F-5 blend.

Table 3. Properties of the compressed tablets.

Tablets Formulations	Thickness (mm) n=10	Weight Variation Test (%) n=20	Hardness (kg/cm ²) n= 10	Friability (%) n=5	Drug Content (%) n=5
F-1	3.96±0.06	199.45±2.64	6.92±0.53	0.59±0.10	97.89±1.64
F-2	3.90±0.03	200.45±2.95	7.97±0.87	0.63±0.20	99.25±0.62
F-3	4.00±0.03	200.30±0.23	7.44±0.64	0.50±0.10	98.99±0.70
F-4	3.98±0.07	202.20±1.38	7.52±0.61	0.74±0.07	97.58±1.46
F-5	3.99±0.07	199.95±1.85	8.04±0.77	0.53±0.08	99.50±0.38
F-6	3.99±0.04	200.70±2.15	8.14±0.42	0.41±0.05	99.45±0.85
F-7	4.01±0.05	201.45±1.05	7.95± 0.68	0.31±0.03	101.32±0.74

All values are expressed as mean±SD.

the individual weight was compared with average weight. The tablet passes the test according to United States Pharmacopoeia if not more than two of the individual weights deviate from the average weight by more than ±7.5% [17].

2.7.2. Drug Content

Ten tablets correctly weighed and powdered. Powder containing diclofenac sodium quantity equal to 50 mg was dissolved in methanol in a volumetric flask and final volume was making up with methanol to 200 ml. From this solution, 5 ml was further diluted to 100 ml with methanol and absorbance was measured at 276 nm. The content was determined by preparing same concentration of diclofenac sodium in the same solvent and absorbance was measured at 276 nm. The % content was determined by [17]:

$$\% \text{Drug content} = \frac{\text{Absorbance of sample} \times \text{average weight of tablet} \times 100}{\text{Absorbance of standard} \times \text{weight of sample}}$$

2.7.3. Hardness

Hardness of 10 tablets was measured by using digital hardness tester (Pharma Test) [18].

2.7.4. Thickness

The thickness of 10 tablets was determined by vernier calipers [18].

2.7.5. Friability

The friability of 10 tablets was determined using Roche Friabilator. Ten tablets were weighed initially (W₀) and transferred into friabilator. The friabilator was allowed to complete 100 revolutions. Again, the tablets

were weighed. Then, % friability was calculated by [16]:

$$\% \text{ Friability} = 100 (1 - W_0/W)$$

Friability (%) of tablets less than 1% were considered satisfactory.

2.8. In vitro drug release studies

The *in vitro* drug dissolution studies of the formulated batches of tablets were carried out using USP apparatus type II (Pharma Test DT-70, Germany). The dissolution medium consisted of 0.1 N HCl pH 1.2 (900 ml) for first 2 h followed by phosphate buffer (pH 7.4) for the next 8 h at temperature of 37±0.5 °C and keeping paddle speed at 50 rpm. At different time intervals, the drug release was measured by drawing 5 ml of sample and replacing by equal volume of medium i.e. 0.1 N HCl pH 1.2. Samples were analyzed by UV-visible spectrophotometer (UV-1601 Shimadzu, Japan) at λ_{max} (276 nm). By putting triplicate (n=3) conducted drug release studies data in pharmacokinetic models, the *in vitro* dissolution rates were analyzed [19].

2.9. Swelling index determination

The swelling index was determined by keeping one tablet from each batch in phosphate buffer pH 7.4 in Petri dish at room temperature. At predefined time intervals, the swollen weight of the tablets was determined by keeping withdrawn tablet on tissue paper. The swelling index (%) was calculated by the following [19]:

$$\% \text{SI} = \frac{\text{Weight of swollen tablet} - \text{Initial weight of tablet} \times 100}{\text{Initial weight of tablet}}$$

Table 4. *In-vitro* release of diclofenac sodium matrix tablets batches containing *Prunus armeniaca* and *Prunus domestica* gums prepared by wet granulation method.

Time (h)	Cumulative % drug release of formulations							Standard
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	
1	21.984	15.685	31.433	15.374	15.716	33.460	16.563	15.307
2	52.189	36.440	62.614	43.685	28.315	56.624	22.462	25.290
4	98.677	92.378	98.677	88.094	57.354	82.460	47.620	45.250
6	98.677	98.803	98.677	93.448	67.779	98.466	73.900	70.600
8	98.677	98.803	98.677	98.708	90.711	98.474	87.450	86.620
10	98.677	98.803	98.677	98.708	98.863	98.380	98.320	99.280

2.10. FT-IR spectroscopy

To study any possible interaction between drug and formulation containing both plant gums, the drug and optimized formulation blend, i.e. batch F-5 (F-5 contain *P. armeniaca* and *P. domestica* gums, diclofenac sodium, HPMC, Avicel and magnesium stearate) compatibility were studied by using IR spectrophotometer (FT-IR Prestige-21, Shimadzu) using pellet of potassium bromide (KBr) for sample holding and expressed in cm^{-1} [10].

3. Results and discussion

3.1. Physical parameters of granules and compressed tablets

The current study was undertaken to formulate and evaluate diclofenac sodium matrix tablets by using plant gums i.e. *P. armeniaca* and *P. domestica*. The granules of different formulation batches prepared (as shown in Table 1) were evaluated for angle of repose (θ), bulk and tapped densities, compressibility index, Hausner’s ratio. The results are shown in Table 2. The angle of repose of batch F-5 and F-7 (36.49 ± 0.65 and 36.86 ± 0.94)

indicate that these two formulations have good flow. Physical characterization of all the batches (shown in Table 3) show acceptable values for all parameters, especially the optimized batch F-5 showed acceptable values of thickness (3.99 ± 0.07 mm), weight variation (199.95 ± 1.85), hardness (8.04 ± 0.77), friability (0.53 ± 0.08), and drug content (99.50 ± 0.38), which all were within the acceptable range [20].

3.2. Kinetic analysis of dissolution

The cumulative amount of all the formulations at different intervals of time was fixed to zero-order kinetics by the least square method to assess the drug release parameters. The data resulted were also fitted to first-order, Higuchi equation, Hixson Crowell and the model developed by Korsmeyer, to find out the mechanism of drug release from these formulations.

The kinetic studies of the formulations showed that formulation F-1, F-3 and standard followed zero order kinetic ($r^2=0.9790$, 0.9980 and 0.9980) and formulations F-4 and F-5 followed the Higuchi model with the values

Table 5. *In vitro* release kinetics of diclofenac sodium matrix tablets containing *Prunus armeniaca* and *Prunus domestica* gums prepared by wet granulation method.

Formulations	Zero	First	Higuchi	Hixson	Korsmeyer		Release mechanism
	Order	Order		Crowell	r ²	N	
	r ²	r ²	r ²	r ²			
F-1	0.9790	0.9090	0.9580	0.9720	0.9870	0.999	non-Fickian
F-2	0.8730	0.7770	0.9320	0.9710	0.9470	0.999	non-Fickian
F-3	0.9980	0.9680	0.9980	0.9830	0.9990	0.960	non-Fickian
F-4	0.9040	0.7870	0.9380	0.9360	0.9580	0.664	non-Fickian
F-5	0.9570	0.8310	0.9780	0.9600	0.9740	0.835	non-Fickian
F-6	0.8960	0.8232	0.8960	0.9730	0.9262	0.471	non-Fickian
F-7	0.9784	0.9491	0.9784	0.9036	0.9633	0.785	non-Fickian
Standard	0.9798	0.9706	0.9798	0.9650	0.9744	0.835	non-Fickian

Table 6. FTIR data interaction.

Bonds/Group	Absorption range in cm^{-1}	Pure Drug	Formulation F-5
- NH	3500-3200	3251.3	3233.7
C-H	3100-2850	3084.0	2917.9
C=O	1780-1630	1742.0	1737.8
C=C	1900-1500	1573.5	1574.0
C-Cl	1280-1350	1281.5	1282.4
C-N	1300-800	1044.1	1029.4
C-C	850-550	844.4	839.0

of $r^2=0.9380$ and 0.9780 , respectively, while formulation batch F-2 followed the Hixson-Crowell model ($r^2=0.9710$). However, to know the exact mechanism of the drug release, the data was fitted into a kinetic model developed by Korsmeyer, which is usually employed for the investigation of drug release mechanism from polymeric matrix systems. According to Korsmeyer's equation, the mechanism of the drug release from the matrix tablets shows that if $n=0.45$, it shows Fickian (case I) release; value $0.45 < n < 1$ for release of non-Fickian or anomalous type; and value of $n=1.0$ indicating case II type of release. In general, case II refers to erosion of the polymeric chain and anomalous transport or non-Fickian refers to both diffusion and erosion controlled-drug release. The values of (n) for all the formulations ranged from 0.664 to 0.999 ($0.5 < n < 1$), that shows anomalous release. Release mechanism is non-Fickian with combination of diffusion as well as erosion controlled-drug release [10].

The release profile of tablets prepared from combination of *P. armeniaca* and *P. domestica* gums are presented in Figure 1 (a) and (b). *in vitro* release of batch F-5 was found to be sustained release extended over 10 h and the rest of formulations showed release (F-1 release was 98.67% in 4 h, F-2 release was 92.37% in 4 h, F-3 release 98.67% in 4 h, and batch F-4 release 93.44% in 6 h). Standard batch extended release up to 10 h. Hence batch F-5 is the optimized one among plant gums based matrix tablets of diclofenac sodium, it was used for comparative study.

3.3. Statistical analysis

Comparison among the prepared formulation batches and reference standard marketed formulation (Voltral SR[®], Novartis Pharma, Pakistan) were made by student T-test at 95% level of confidence (14 Statistical software Manitab Release). With respect to the drug release, batch F-5 did not significantly differ from F-7 and standard marketed formulation (Voltral SR[®], Novartis Pharma, Pakistan) but other formulation batches differ a lot when compared to the standard marketed formulation for value of $p < 0.05$.

3.4. Swelling index of formulated batches

The swelling indexes of the formulations are directly proportional to the concentration of gum. Formulation batch F-5 shows 65.64% swelling index at the end of the 10th h, and after 5 h there is decrease in swelling index of matrix tablet due to the erosion of surface layer, while for formulation F-7 found to be 80.06% and decrease in swelling index 4-5 h due to erosion (shown in Figure 2). These values of swelling index dictate that these formulations showed good swelling indexes.

3.5. Drug excipient compatibility studies

Drug excipient compatibility studies were carried out using IR spectroscopy. IR spectra of the drug (diclofenac sodium) and that of optimized formulation F-5 (drug and plant gums mixture) were analyzed. The studies revealed that there was no significant interaction between drug and the optimized batch (i.e. batch F-5) containing plant gums. The IR spectra of pure diclofenac sodium

and its physical mixtures with other excipients are shown in Figures 3(a), and 3(b) and interpretation were listed in Table 6.

4. Conclusion

Both plant gums (P. armeniaca and P. domestica gums) based diclofenac sodium matrix tablets have better drug release profile and comparable sustaining action of drug release when used in combination i.e. ratio 1:1. Formulation batch F-5 release show that 98.86% of drug releases at the end of 10 h, which is compared with standard marketed formulation (Voltral SR[®], Novartis Pharma, Pakistan). Hence, both plant gums of P. armeniaca and P. domestica as a natural excipient can be used as matrix former in tablet formulations.

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