

Comparative studies of binding potential of *Prunus armeniaca* and *Prunus domestica* gums in tablets formulations

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Abstract: The current study was undertaken to compare the binding potential of *Prunus armeniaca* L. and *Prunus domestica* L. gums in tablets' formulations. Tablet batches (F-1 to F-9) were prepared Diclofenac sodium as model drug using 5%, 7.5% and 10% of each *Prunus armeniaca* L., *Prunus domestica* L. gums as binder. PVP K30 was used as a standard binder. Magnesium stearate was used as lubricant. Flow properties of granules (like bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose) as well as the physical parameters of compressed tablets including hardness, friability, thickness and disintegration time were determined. Flow parameters of granules of all the batches were found good. Physical parameters (drug content, weight variation, thickness, hardness, friability, disintegration time) of formulated tablets were found within limit when tested. The dissolution studies showed that tablets formulations containing each *Prunus domestica* showed better binding capacity compared to *Prunus armeniaca* gum. The binding potential increased as the concentration of gums increased. The FTIR spectroscopic investigation showed that the formulations containing plant gum are compatible with the drug and other excipients used.

Keywords: *Prunus armeniaca* gum, *Prunus domestica* gum, binders, diclofenac sodium tablets.

INTRODUCTION

Gum is a metabolic by-product obtained from plants. The plants derived gums either absorb water to form a viscous solution or swells up by water. Among the advantages are: economic one and easily available (Sarjoni *et al.*, 2010). Plant derived natural polysaccharides are more suitable pharmaceutical excipients due to availability, renewability, stability, non-toxicity and are, therefore, widely used in modified release dosage forms as matrix formers (Beneke *et al.*, 2009; Nep and Conway, 2010). Plants derived gums obtained have role as a disintegrant, an emulsifying agent, a suspending agents, as a binder *Prunus domestica* L. (Rosaceae), small to medium size trees, found throughout Pakistan including Azad Jammu and Kashmir region (Gilani *et al.*, 2011). The gum obtained from the said plant is used as a laxative, a tonic and vermifuge (Abbassi, 2009; Lardos, 2011).

Diclofenac sodium is a non-steroidal anti-inflammatory drug, a poorly water drug frequently used as analgesic, antipyretic, anti-inflammatory and for the long-term management of rheumatoid arthritis (Ganish *et al.*, 2010).

The study aimed to compare the binding potential of both plant gums in formulation of Diclofenac sodium tablets.

MATERIALS AND METHODS

Materials

Diclofenac sodium, Avicel pH 101, Aerosil, magnesium

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stearate and PVP K30 were kind gift of Prays Pharmaceuticals (Pvt.) Ltd, Islamabad, Pakistan. Hydrochloric acid, Methanol, sodium hydroxide, Potassium dihydrogen phosphate (Merck, Germany) and acetone (Sigma Aldrich, Germany) were purchased from Musaji and Sons, Khyber Bazaar, Peshawar, Pakistan.

Methods

Collection of *prunus armeniaca* and *prunus domestica* gums

Gums were collected from the bark of *Prunus armeniaca* L. and *Prunus domestica* L. (Family Rosaceae) plants respectively, from Sheringal valley of Dir Upper region of Khyber Pakhtunkhwa, Pakistan. After collection, gums were dried in oven at 60°C followed by hydration to remove extraneous materials by straining through a muslin cloth. The gums were precipitated from the solution using absolute acetone. The precipitate was separated, dried in oven at 50°C and stored in a container tightly closed to utilize in formulating Diclofenac sodium tablets.

Preparation and evaluation of granules

Granules were prepared using *Prunus domestica* L. and *Prunus armeniaca* L. gums in different ratios as binder, Diclofenac sodium as an active drug and PVP K30 as a standard binder. Total weight of tablet was kept 200mg. Diclofenac sodium, Avicel pH 101, Aerosil and gum were separately mixed 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 hours and were then passed through mesh

18. Finally magnesium stearate was added as lubricant to each batch (as shown in table 1).

Evaluation of granules

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

Bulk density

Granules of known weight (m) were poured in 10 ml graduated cylinder, bulk volume (V_0) was noted and bulk density was calculated (g/cc) by formula: (Chandramouli *et al.*, 2012) Bulk Density= weight of granules/Bulk volume.

Tapped density

The graduated cylinder (10ml) containing known weight (m) of granules was tapped on a tough 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 (Bamiro *et al.*, 2010).

Compressibility index

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

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

Where T_d is tapped density and B_d is bulk density.

Hausner's ratio

It was calculated by the following formula: (Shivan and 2010)

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

Where T_d is tapped and B_d is bulk density.

Angle of repose

It was determined by filling powder in a funnel (10gm). Then, the funnel was opened to release the powder, form a conical heap on the paper. The values were calculated by formula, (Shivan and, 2010)

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

Where h = height of the heap

r = radius of the heap

Preparation of diclofenac sodium 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).

Evaluation of tablets

Average weight

Twenty (20) tablets were weighed by analytical balance (Sartorius BL 2105, Germany) after compression, then average weight and standard deviation was determined (USP, 2004).

Drug content

Ten (10) tablets were accurately weighed and crush to powder. Powdered amount (equal to 50mg Diclofenac

sodium) was shaken with 60ml of methanol in a 200ml volumetric flask and final volume made up with methanol, 5ml of this solution was further diluted to 100 ml with methanol and absorbance was measured at 276 nm. The content was determined by dilution to same concentration of 50mg Diclofenac sodium (active) in methanol and absorbance was measured at 276 nm. The % content was determined by: (Shingala, 2010)

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

$$\text{Absorbance of standard} \times \text{weight of sample}$$

Hardness

Hardness of 10 tablets was determined by using digital hardness tester (Pharma Test) and mean $\pm$ S.D. of each formulation mentioned in table 3 (Shingala, 2010).

Thickness

The thickness of tablets (10in number) was determined through Vernier caliper and their average were calculated (Shingala, 2010).

Friability

Using Roche Friabilator, the friability of ten (10) tablets was determined. Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at a speed of 25rpm for 4 minutes or was run up to complete 100 revolutions. The tablets were weighed again (W). The % friability was then calculated, by using formula: (Shivan and, 2010)

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

Where W_0 =initial weight of 10 tablets

W = weight of 10 tablets after 100 revolutions

%Friability of tablets less than 1% were considered acceptable.

Disintegration time

The Disintegration time was determined as per USP/NF procedure, in simple words, 0.1N HCl (as medium) maintained at temperature i.e. $37 \pm 2^\circ\text{C}$. Tablets (six in number) were randomly selected from each batch. Tablets were placed in each of the cylindrical tubes of the basket but no disc was used. The time taken for each tablet to break up into tiny particles and pass out through the mesh (screen) was noted (Satyam *et al.*, 2010).

In-vitro dissolution studies

In-vitro dissolution test of all the prepared tablets was performed using USP dissolution apparatus II (paddle apparatus) Phosphate buffer (pH 6.8) as dissolution medium at temperature $37 \pm 2^\circ\text{C}$ and paddle rotation speed 50 rpm. At regular intervals (10 minutes) up to 1hour, samples were withdrawn, replacing equal amount of fresh dissolution medium. Drug release (%) was calculated by analyzing samples on UV spectrophotometer at 276 nm (Satyam *et al.*, 2012).

Release kinetics

Different kinetic models (zero-order, first-order, Higuchi's and Korsmeyer's equation) were applied to interpret the release profile (the order and mechanism of Diclofenac sodium release) from tablet. To understand the mechanism of release Korsmeyer's-Peppas model was applied, the value of "n" less than 0.45 shows the Fickian Diffusion, between 0.45 and 0.89 indicates the non-Fickian or anomalous diffusion, 0.89 indicates the case-II transport and above 0.89 shows super case diffusion (Siva et al., 2012).

FTIR studies

For any possible interaction between drug and the plant gums used, FTIR spectroscopic analysis were carried out. The drug, plant gums and optimized formulation blends containing each gum, compatibility were studied by using IR spectrophotometer (Nicolet FTIR spectrophotometer, Thermo scientific Nicolet, USA). A small amount of Diclofenac sodium, plant gum and formulation blend were respectively placed directly on the piece (germanium) of the IR spectrometer with applying constant pressure, data of infrared absorbance were collected over the wave number ranged from 4000 cm^{-1} to 400 cm^{-1} and was expressed in cm^{-1} (Nazneen et al., 2012).

RESULTS

The prepared granules were evaluated flow properties. The Carr's index values were found in range from 8.91 ± 0.91 to 16.19 ± 0.56 , angle of repose values resulted were 30.16 ± 0.47 to 35.23 ± 0.63 . All the results showed good flow of the granules as shown in table 2.

Three batches of tablets prepared for each gum in different concentrations were evaluated for parameters like hardness (kg/cm^2), weight variation (%), thickness (%), friability (%), disintegration time (min) and drug content (%). Hardness were found in range of 7.50 ± 0.63 to 7.95 ± 0.63 kg/cm^2 , weight variation 199.25 ± 3.89 to 201.50 ± 3.17 , friability values are in acceptance range 0.24 ± 0.04 to 0.67 ± 0.02 , disintegration time were less than 15 min. All these results are indicated in table 3.

In Vitro dissolution studies

In-vitro dissolution in phosphate buffer pH 6.8, batch F-2 (containing 7.5% *Prunus domestica* gum) release showed 78.12% of drug releases at the end of 50min, which is compared with F-5 (containing 7.5% *Prunus armeniaca* gum) releasing 76.87% at the end of 30min, F-8 batch (containing 7.5% standard binder PVP K30) released 72.20% drug at the end of 20 minutes. While using 10% of *Prunus domestica* gum formulated batch (F-3) 82.18%

Table 1: Formulation of diclofenacsodium tablets using *Prunus armeniaca* and *Prunus domestica* gums

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Diclofenac sodium	50	50	50	50	50	50	50	50	50
PDG (Binder)	10	15	20	---	---	---	---	---	---
PAG (Binder)	---	---	---	10	15	20	---	---	---
Avicel pH 101	133	128	123	133	128	123	133	128	123
PVP K30 (Binder)	---	---	---	---	---	---	10	15	20
Aerosil	4	4	4	4	4	4	4	4	4
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total weight	200	200	200	200	200	200	200	200	200

Key: ---means absent, PDG= *Prunus domestica* gum, PAG= *Prunus domestica* gum

Table 2: Evaluation of granules

Batches	Flow properties of granules of various batches				
	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner ratio	Angle of repose (*)
F-1	0.577 ± 0.00	0.636 ± 0.01	9.27 ± 0.59	1.09 ± 0.01	32.10 ± 0.31
F-2	0.592 ± 0.01	0.662 ± 0.01	10.61 ± 0.54	1.11 ± 0.00	31.30 ± 0.12
F-3	0.601 ± 0.01	0.660 ± 0.01	8.91 ± 0.94	1.09 ± 0.01	30.16 ± 0.47
F-4	0.567 ± 0.00	0.637 ± 0.00	10.98 ± 0.01	1.12 ± 0.00	35.14 ± 0.24
F-5	0.591 ± 0.01	0.663 ± 0.02	10.74 ± 0.54	1.11 ± 0.00	33.54 ± 0.29
F-6	0.570 ± 0.00	0.646 ± 0.00	11.39 ± 0.64	1.12 ± 0.00	34.06 ± 0.46
F-7	0.488 ± 0.00	0.582 ± 0.00	15.88 ± 0.72	1.18 ± 0.00	35.23 ± 0.63
F-8	0.491 ± 0.00	0.580 ± 0.00	15.33 ± 0.84	1.17 ± 0.01	33.50 ± 0.33
F-9	0.494 ± 0.00	0.590 ± 0.01	16.19 ± 0.56	1.18 ± 0.00	31.60 ± 0.62

*All the values are expressed as mean $\pm$ SD

drug release was extended up to end of an hour, the same concentration of *Prunus armeniaca* gum used formulation (F-6) released 90.55% drug at the end of 50 minutes (as results shown in fig. 1).

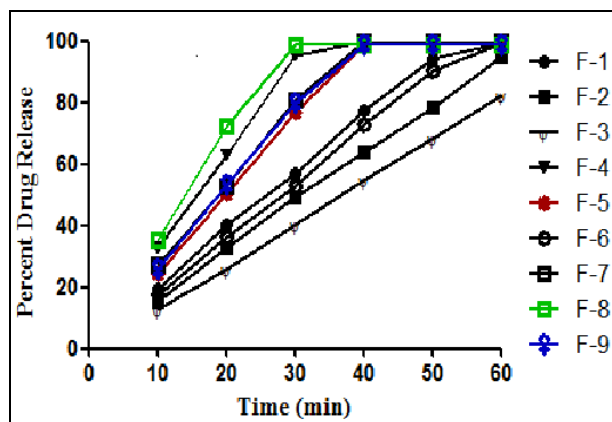


Fig. 1: In vitro Drug Release of Formulations (F-1 to F-9)

In vitro release kinetics

Different kinetic models (zero-order, first-order, Higuchi's and Korsmeyer's equation) were applied to interpret the release profile (the order and mechanism of Diclofenac sodium release) from tablet.

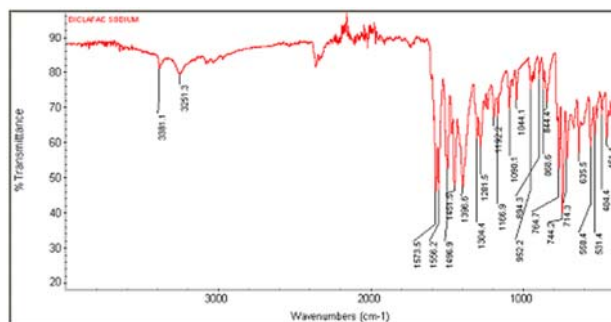


Fig. 2: FTIR spectra of Diclofenac sodium

The drug release rate kinetic data for all the model was evaluated using regression coefficient analysis. The in-vitro release profiles of drug from all these formulations showed good linearity ($r^2=0.8367$ to 0.9890 and $r^2=0.7445$ to 0.9740) by putting in Higuchi and Hixson Crowel models respectively. However, these models were not sufficient to explain the drug release phenomena due to combination of swelling and erosion of matrix. The dissolution data was also put into Korsmeyer model, which is frequently used to explain the behaviour of drug release from polymeric system. The formulation showed higher linearity ($r^2=0.8882$ to 0.9970) as evident from table 4.

Drug excipients compatibility studies

Drug and excipients compatibilities studies were carried out by using IR spectroscopy. IR Spectra of Drug (Diclofenac sodium) and tablets formulations containing

Prunus domestica L. and *Prunus armeniaca* L. gums were analyzed. The studies revealed that there was no significant interaction between drug and batches containing plant gums. The IR spectra of pure Diclofenac sodium showed distinct peaks at 3251.3cm^{-1} ($-\text{NH}$), 3084.0cm^{-1} (CH), 1573.5cm^{-1} ($\text{C}=\text{C}$), 1281.5cm^{-1} ($\text{C}-\text{Cl}$), 1044.1cm^{-1} ($\text{C}-\text{N}$) and 844.4cm^{-1} ($\text{C}-\text{C}$). Its physical mixtures with other excipients including *Prunus domestica* and *Prunus armeniaca* gums are shown in figs. 2, 3 and 4. Hence no major change in peaks of Diclofenac sodium tablets formulations containing both gums, so gums are compatible with drug and other excipients used.

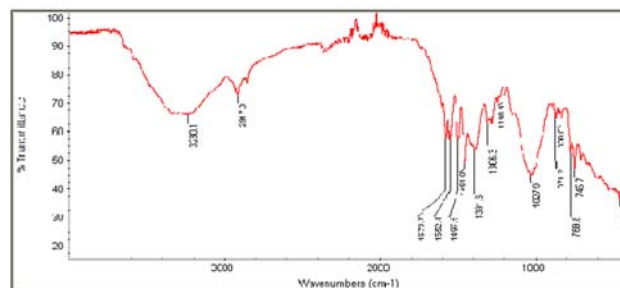


Fig. 3: FTIR spectra of formulation blend containing *Prunus armaciaca* guma

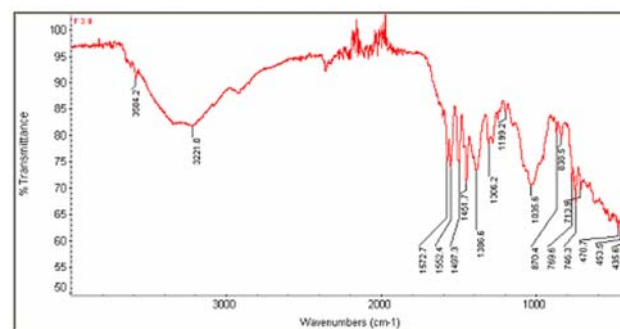


Fig. 4: FTIR spectra of formulation blend containing *Prunus domestica* gum

DISCUSSION

All the results showed good flow of the granules when the flow parameters (angle of repose, bulk density, tapped density and Hausner's ratio) were tested.

Three batches of tablets prepared for each gum in different concentrations were evaluated for parameters like hardness (kg/cm^2), weight variation (%), thickness (%), friability (%), disintegration time (min) and drug content (%). Hardness were found in range of 7.50 ± 0.63 to $7.95 \pm 0.63 \text{ kg}/\text{cm}^2$, weight variation (199.25 ± 3.89 to 201.50 ± 3.17) were within limit (± 7.5). Friability values are in acceptance range, disintegration time were less than 15 min fulfilling the pharmacopoeial limits for uncoated tablets, drug content ranged from 98.02 ± 0.75 to 101.10 ± 1.75 (limit is 90-110%). All these results are indicated in table 3.

Table 3: Evaluation of diclofenac sodium tablets

Tablets batches	Hardness (Kg/cm ²)	Weight variation (%)	Thickness (mm)	Friability (%)	Disintegration time* (min)	Drug content (%)
F-1	7.50±0.63	200.80±3.24	4.32±1.04	0.67±0.02	4 min, 40 sec	98.02±0.75
F-2	7.83±0.58	200.30±3.15	4.32±1.08	0.54±0.05	9min, 10 sec	98.99±0.65
F-3	7.95±0.68	200.80±3.22	4.31±1.12	0.42±0.03	14min, 40sec	100.34±1.09
F-4	7.85±0.84	201.25±3.34	4.01±0.03	0.37±0.01	3min, 40sec	99.40±1.85
F-5	7.73±0.68	201.22±3.63	3.99±0.03	0.32±0.02	8min, 20sec	101.10±1.81
F-6	7.72±0.64	202.22±3.31	4.01±0.04	0.24±0.04	13min, 20sec	99.59±1.81
F-7	7.94±0.63	199.25±3.89	4.36±1.13	0.69±0.04	4min, 36sec	98.62±0.72
F-8	7.77±0.51	201.50±3.17	4.34±1.03	0.60±0.05	9min, 10sec	100.42±0.96
F-9	7.65±0.65	200.48±3.65	4.30±0.91	0.45±0.05	11min, 05sec	99.36±1.04

All the values are expressed as mean±SD except data denoted by asterisk (*)

Table 4: *In vitro* release kinetics of diclofenac sodium tablets (F-1 to F-9)

Formulations	Zero order	First order	Higuchi	Hixson Crowell	Korsmeyer		Release Mechanism
	R ²	R ²	R ²	R ²	R ²	N	
F-1	0.977	0.897	0.989	0.792	0.992	0.9579	Super case II
F-2	0.996	0.927	0.9798	0.7445	0.9983	0.9984	Super case II
F-3	0.999	0.947	0.979	0.974	0.997	0.9987	Super case II
F-4	0.742	0.69	0.8367	0.8592	0.8882	0.6617	Non-Fickian
F-5	0.857	0.787	0.9222	0.88	0.9467	0.8327	Non-Fickian
F-6	0.99	0.719	0.989	0.9451	0.9968	0.9991	Super case II
F-7	0.842	0.775	0.9124	0.8789	0.94	0.7686	Non-Fickian
F-8	0.789	0.705	0.8761	0.8771	0.8949	0.6074	Non-Fickian
F-9	0.84	0.763	0.9133	0.8829	0.9357	0.8894	Non-Fickian

***In vitro* dissolution studies**

When compared to the PVP K-30 as binder used in concentration of 10% (F-9 batch), both gums were found to be efficient binder and in comparison of both plant gums *Prunus domestica* could be used in lower concentration (7.5%) as tablet binder.

***In vitro* release kinetics**

The formulations (F-1, F-2, F-3 and F-6) followed super case II type of release, which refers to the erosion of the polymeric chain and anomalous transport. The batches (F-4, F-5, F-7, F-8 and F-9) followed non-Fickian release mechanism, which refers to the combination of diffusion and erosion as in table 4.

CONCLUSIONS

Both *Prunus armeniaca* and *Prunus domestica* plant gums showed excellent binding ability as evident from dissolution profiles. While comparing both plant gums with each other *Prunus domestica* was found to better binder in low concentration i.e. 7.5% as compared to *Prunus armeniaca* gum. Hence, *Prunus domestica* gum and *Prunus armeniaca* L., natural excipients, can be used as binders in tablet formulations. The release profiles showed that both gums could be used in combination and with semi-synthetic polymer in sustained release tablets.

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