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B.D L Narayana D.Lokesh, **K.Sudheer**, **S.NagaBhaskar** , **Syed. Sharif**. **P.Sivannarayana***

SIDDHARTH INSTITUTE OF PHARMACY, KANTEPUDI (V), SATTENAPALLI (M), GUNTUR (Dt.)-522438, ANDRA PRADESH.

DESIGNING AND EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX TABLETS USING ABELMOSCHUS ESCULENTUS MUCILAGE

ABSTRACT

The aim of this work is to design and evaluate diclofenac sustained release matrix tablets using Abelmoschus esculentus mucilage (okra gum). Diclofenac is a non-steroidal anti-inflammatory drug used in the long-term treatment of Rheumatoid arthritis. The biological half life of diclofenac is about 1-2 hr; therefore it requires multiple dosing to maintain therapeutic drug blood level. The most frequent side effects of diclofenac on long term administration are gastrointestinal disturbances, peptic ulceration. Hence an attempt was made to formulate a sustained release formulation with increased patient compliance and decreased signs of adverse effects.

KEYWORDS: DICLOFENAC SODIUM, SUSTAINED RELEASE, MUCILAGE, ABELMOSCHUS ESCULENTUSS.

INTRODUCTION

Diclofenac (marketed under many brand names, see below: Trade names) is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in certain conditions.

The name is derived from its chemical name: 2-(2,6-dichloranilino) phenylacetic **ac**id.

In the United Kingdom, India, Brazil and the United States, it may be supplied as either the sodium or potassium salt, in China most often as the sodium salt, while in some other countries only as the potassium salt. Diclofenac is available as a generic drug in a number of formulations. Over-the-counter (OTC) use is approved in some countries for minor aches and pains and fever associated with common infections.

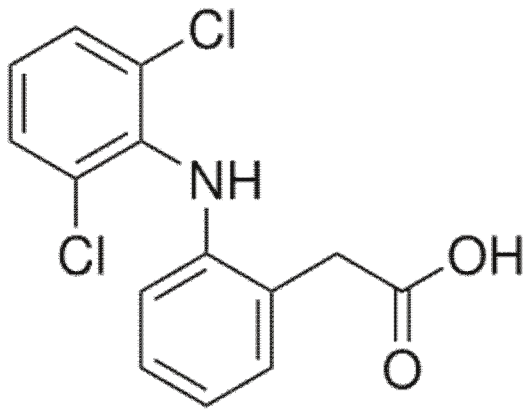


Figure.1 Structure of Diclofenac

Diclofenac is used to treat pain, inflammatory disorders, and dysmenorrhea.[1] Inflammatory disorder may include musculoskeletal complaints, especially arthritis, rheumatoid arthritis,polymyositis, dermatomyositis, osteoarthritis, dental pain, TMJ, spondylarthritis, ankylosing spondylitis,gout attacks,[2] and pain management in cases of kidney stones and gallstones. An additional indication is the treatment of acute migraines.[3] Diclofenac is used commonly to treat mild to moderate post-operative or post-traumatic pain, in particular when inflammation is also present,[2] and is effective against menstrual pain and endometriosis.

As long-term use of diclofenac and similar NSAIDs predisposes for peptic ulcer, many patients at risk for this complication are prescribed a combination (Arthrotec) of diclofenac and misoprostol, a synthetic prostaglandin(PGE1) analogue, to protect the gastric mucosa.

Arthrotec (diclofenac andmisoprostol) 50 mg tablets

An external, gel-based formulation containing 3% of diclofenac (Solaraze) is available for the treatment of facial actinic keratosis caused by over-exposure to sunlight. Some countries have also approved the external use of diclofenac 1% gel to treat musculoskeletal conditions.

In many countries eye-drops are sold to treat acute and chronic non-bacterial inflammations of the anterior part of the eyes (e.g., postoperative states). A common brand name is Voltaren-optha.

Investigational uses

Diclofenac is often used to treat chronic pain associated with cancer, in particular if inflammation is also present (Step I of the World Health Organization (WHO) Scheme for treatment of chronic pain). Good results (sometimes better than those with opioids) have been seen in female breast cancer and in the pain associated with bony metastases.

Dyloject (diclofenac) 2 mL for IV and IM administration

Diclofenac can be combined with opioids if needed. Combaren, a fixed combination of diclofenac and codeine (50 mg each), is available for cancer treatment in Europe. Combinations with psychoactive drugs such as chlorprothixene and/or amitriptyline have also been investigated and found useful in a number of cancer patients.

Fever due to malignant lymphogranulomatosis (Hodgkin's lymphoma) often responds to diclofenac. Treatment can be terminated as soon as the usual treatment with radiation and/or chemotherapy causes remission of fever.

Sintofarm (diclofenac) forsuppository administration

Diclofenac has been found to increase the blood pressure in patients with Shy-Drager syndrome anddiabetes mellitus. Currently, this use is highly investigative and cannot be recommended as routine treatment.

Diclofenac has been found to be effective against all strains of multi drug resistant E. coli, with a MIC of 25 micrograms/mL. Therefore, it may be suggested that diclofenac has the capacity to treat uncomplicated urinary tract infections (UTI) caused by *E. coli*.[4] It has also been shown to be effective in treating Salmonella infections in mice[5] and is under investigation for the treatment of tuberculosis.[6]

Diclofenac is an antiuricosuric.[7]

Okra

Botany

Okra is a coarse, erect, branched, more or less hairy, annual herb, 0.6 to 1.5 meters high. Leaves are long-petioled, orbicular or orbicular-ovate, about 25 centimeters long or less; with a heart-shaped base; the margins, 3- to 5-lobed. Petioles are equal to the blade in length or longer. Flowers are axillary and solitary; corolla, large and yellow, and inside, deep purple at the base. Fruit is elongated, 10 to 25 centimeters long, 1.5 to 3 centimeters in diameter, tapering to a blunt point and containing rows of rounded, kidney shaped seeds.

Distribution

- Cultivated for its edible fruit.
- Nowhere naturalized.
- Pantropic.

Figure.2

Constituents

1. Fruit contains abundant pectin; mucilage; starch; some fat, 4%; water, 80.7%; and ash, 1.41%.
2. Seeds yield: palmitic acid, 27.33%; stearic acid, 2.75%; arachidic acid, 0.05%; oleic acid, 43.74%; linolic acid, 26.62%; unsaponifiable matter, 0.37%.
3. Roots yield gum, 16%; and the seeds yield vitamin C.
4. Distillation of leaves with water yield an essential oil, which in time solidifies as a crystalline camphor allied to menthol and called 'Basil-camphor.'

Materials and Methods:

S.No:	TEST	EQUIPMENT
1.	Weight variation	High Precision Balance

2.	Thickness	Vernier Callipers
3.	Hardness	Monsanto Hardness Tester
4.	Friability	Roche Friabilator
5.	Dissolution	USP Type II Dissolution apparatus
6.	Disintegration	USP Disintegration Apparatus
7.	Assay	EI Double beam UV-Visible Spectrophotometer model no: 1372

TABLE.1

Extraction of mucilage[28]:

The fresh fruits of Abelmoschus esculentus *(5kg)* are collected and washed with water. Then they are crushed mechanically with motor and pestle and soaked in water for 5-6hrs. Then they are boiled in a stainless steel container at burner temperature for 2-3hrs. After boiling, keep aside for 1hr, for complete release of mucilage into the water. Then the solution is passed through muslin cloth to remove the marc. To the volume of solution obtained, add 3 times the amount of acetone, to precipitate the mucilage. Then the precipitate is dried in oven at 50-60 ◦c for 2hrs for complete removal of moisture. After complete removal of moisture it was collected, powdered with the help of motor and pestle. And it was passed through sieve no.80. The mucilage obtained is stored in a air tight container.

For 5kg fruits of Abelmoschus esculentus we have obtained 13.54gms of mucilage. An average 2.708gms of mucilage is obtained per 1kg fruits.

EVALUATION TESTS FOR MUCILAGES[29]

- ✓ Treat the test solution with ruthenium red solution pink colour is obtained.
- ✓ Treat the test solution with thionine solution after 15 minutes wash with alcohol. Mucilage forms violet red colour.
- ✓ Treat the test solution with Chinese ink, transparent spherical dilated fragments on black background are observed.
- ✓ Take 10ml of aqueous solution and add 25ml of absolute alcohol with constant stirring. A precipitate is formed which is dried in air and examined for its swelling properties.

ANGLE OF REPOSE(ø)	TYPE OF FLOW
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

TABLE .2

Flow properties of mucilage

Parameters	Value
Bulk density(g/ml)	0.597
Tapped density(g/ml)	0.781
Carr's index (%)	23.55
Hausner's ratio	1.308
Angle of repose(0)	24.98

TABLE .3

FORMULATIONS

Ingredients(mg)	F1	F2	F3	F4	F5
Diclofenac	100	100	100	100	100
Okra gum	20	40	60	80	100
MCC(Avicel)	125	105	85	65	45
Magnesium sterate	5	5	5	5	5
Total weight	250	250	250	250	250

TABLE.4

Drug: Gum in 1:0.2, 1:0.4, 1:0.6, 1:0.8, 1:1 ratios.

Drug: MCC (Avicel) in 1:1.25, 1:1.05, 1:0.85, 1:0.65, 1:0.45 ratios.

Drug: Magnesium sterate in 1:0.05 for all formulations.

TABLET PREPARATION

1. All the ingredients were weighed accurately using digital weighing balance and were passed through a #100 sieve.
2. The binder solution was prepared by dissolving okra gum in hexane as solvent.
3. All the excipients are blended together. Then all the excipients, including drug were mixed in the binder solution according to their respective formulations (F1, F2, F3, F4 and F5).
4. The powder mixture was kept in hot air oven at 60^{o}c for complete evaporation of hexane.
5. The tablets were prepared by direct compression method by using 10mm biconvex punches at the pressure of 35psi.

DISSOLUTION STUDY [32]

Acidic Stage: (P^H 1.2)

Medium	0.1N HCl
Type of apparatus	USP - II (paddle type)
RPM	100
Volume	1000ml
Temperature	37^{o}C± 0.5
Time	2hrs

TABLE.5

Buffer Stage: (P^H 6.8)

Medium	6.8 pH phosphate buffer
Type of apparatus	USP - II (paddle type)
RPM	100
Volume	900ml
Temperature	37°C± 0.5
Time	12 hours
Withdrawal of sample	30 min, 1hr, 2hr,4hr, 6hr,8hr, 10hr,12hr

TABLE.6

Absorbance was found for the samples withdrawn using phosphate buffer as blank and λ-max at 276 nm. Dilutions were made as required.

Preparation of Reagents[33]

0.1 N HCl:

Take 8.5 ml of conc. HCl and dilute to 1000 ml with distilled water.

6.8 pH Phosphate buffer:

50 ml of 0.2 M potassium dihydrogen phosphate and 22.4 ml of 0.2 M NaOH are taken and the volume is made up to 200 ml with distilled water.

Calibration curve of Diclofenac

The calibration curve is a plot of how the instrumental response, the so-called analytical signal, changes with the concentration of the analyte (the substance to be measured).

Procedure:

1. A series of standards across a range of concentrations near the expected concentration of analyte in the unknown are prepared.
2. The concentrations of the standards must lie within the working range of the technique (instrumentation) we are using.
3. Analyzing each of these standards using the chosen technique will produce a series of measurements.
4. A plot of instrument response (Absorbance) vs analyte concentration will show a linear relationship.
5. We can measure the response of the drug using the calibration curve; can *interpolate* to find the concentration of analyte.

FIGURE.3 UV Visible Spectrophotometers

RESULTS AND DISCUSSION

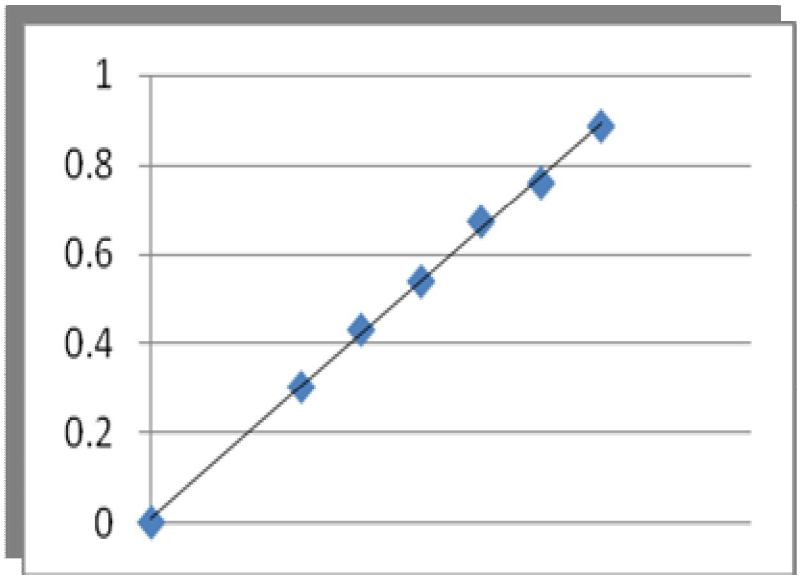
S.No	Formulation	Weight variation (%)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
1.	F1	1.9	3.9	3.5	0.50
2.	F2	3.7	3.8	4.0	0.45
3.	F3	4.6	4.0	3.5	0.50
4.	F4	2.4	3.9	3.5	0.78
5.	F5	3.5	3.8	4.0	0.65

Table.7 PHYSICAL PROPERTIES OF TABLETS

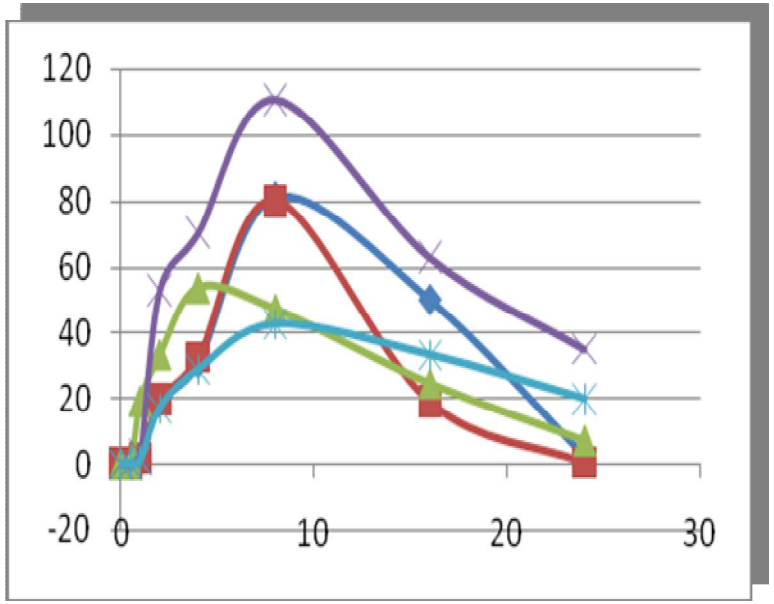
S.No	Concentration(µg/ml)	Absorbance at 276nm
1.	0	0
2.	50	0.302
3.	70	0.431

4.	90	0.539
5.	110	0.673
6.	130	0.761
7.	150	0.888

Table.8 Standard graph for Diclofenac sodiu



Graph.1 Calibration curve for Diclofenac sodium



Graph.2 Drug releasing profile

The formulation development of diclofenac sodium sustained release matrix tablets was done with different concentrations of Abelmoschus esculentus mucilage as a binding agent. Various evaluation tests were conducted for the formulated batches. The mucilage has been checked for some evaluation parameters to know the flow properties, Bulk density, Tapped density, Compressibility index, Hausner's ratio are calculated to know the flow properties of the mucilage.

The release profile of the all formulation is shown in the Graph.2 The sustained release matrix tablets of Diclofenac sodium prepared with Abelmoschus esculentus mucilage(okra gum) in various concentrations released the drug in various manners. The F1 released 81% of drug at 6 hrs. F2, F4 and F5 released 80%, 110% and 42% respectively at 8hrs .F3 released 53% drug at 4hrs.

The order of cumulative percentage drug released was F4>F1>F2>F2>F3>F5 with values of 110, 81, 80, 53, 42 respectively.

The present study revealed that the formulation F4 with Drug: Gum ratio of (1:0.08) should greater cumulate percentage drug release and the formulation F5 with Drug: Gum ratio of (1:1) should lower cumulative percentage drug release.

CONCLUSION

The present investigation revealed that Abelmoschus esculentus leaves mucilage appears to be suitable for use as a release retarding in the formulation of sustained release matrix tablets because of its good swelling, good flow and suitability for matrix formulation .from the dissolution study, it was concluded that dried Abelmoschus esculentus mucilage can be used as an excipient for making sustained release matrix tablets of diclofenac.

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