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NATURAL POLYMER AS MATRIX FORMING AGENT: INDIAN CHERRY

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ABSTRACT

The matrix forming agent like Indian cherry shows sustained release property in tablet which obtained naturally from the fruits of cordia dichotoma having family-Boraginaceae. The gum is initially white in color but changes to brownish black on exposure to atmosphere. It is sparingly soluble in water but swells in contact with water, giving a highly viscous solution. swelling like mechanism to release the drug for prolong period of time by matrix formation. Also used as binder, lubricant, diluents, matrix former, film former, adhesive, disintegrant in tablet & shows acid resistant property suitable for thermo-sensitive drugs.
SYNONYMS
Bhokar (Marathi), Gunda (Hindi), Lasura (Nepali), Lasoda, Tenti, Della\textsuperscript{[1,5,6]} etc.

INTRODUCTION
The cordia natural polysaccharides are being widely used in the pharmaceutical industry due to their advantageous properties such as low cost, relative abundance and biocompatibility as compared to their synthetic ones. These are used as gelling agent, binding agent, bulking agent, lubricating agent, sweetening agent, flavouring agent, and suspending agent. Polymers derived naturally can be used in the formulation of sustained release dosage form by which desired properties can be obtained for the finished drug product\textsuperscript{[4,5]}

In sustained release dosage forms, release of drug is sustained due to the swelling property of these polymers by making a gel like thick layer which retard the release of drug. These polymers can be hydrophilic or hydrophobic in nature\textsuperscript{[4,5,6]}. Pharmaceutical excipients may be defined as the additives used to convert pharmacologically active substances into pharmaceutical dosage form suitable for administration to the patients.

Natural Gums are naturally occurring polysaccharides found in plants to which multiple sugar units are linked together to form large molecules. These gums are pathological products formed by breakdown of cell following injury to the plant (extracellular formation: Gummnosis). Hence, Natural gums has its application in the pharmaceutical and food industries which are considered to be safe for human consumption. Mucilage is the metabolized product, produced within the cell and/or produced without injury to the plant. Mucilage is composed of polysaccharide uranides and proteins. Gums are pathological products, while mucilage is the physiological product which is the main difference between the gum and mucilage. Gum has the property of swelling in aqueous media forming a highly viscous solution while mucilage forms slimy mass in water. Both gum and mucilage are produced by plants during injury which are amorphous, translucent. Mucilage, resin, cellulose and gum are differentiated by the condensation of hexane and pentose\textsuperscript{[7,8,9]}

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in development a sustained release system. For sustained release systems, the oral route of drug administration has received the most interest as it is natural, uncomplicated, convenient and safer route. Matrix tablets were prepared by direct compression method. Mucilages are composed of heterogenous polysaccharide complexes formed from the sugars, arabinose, galactose, glucose, mannose, xylose and uronic acid units. Mucilages possess a variety of pharmaceutical properties, which make them useful as additives in pharmaceutical
preparations and in present investigations, mucilages plays important role in design of formulations [10, 11].

*Cordia dichotoma* Forst. Fruits are 1.3-2.5 cm long globose or ovoidglossy, yellowish brown, pinkish or nearly black when ripe, usually single seed surrounded by a transparent, sticky and sweet edible pulp. Conventionally *Cordia dichotoma* fruits were used as vegetables, formaking pickles and glues. The other parts of the plant like leaves and bark have been reported for various pharmacological activities such as analgesic, anti-inflammatory, antioxidant, antitumour etc. Qualitative analysis for the presence of plant constituents such as carbohydrates, alkaloids, glycosides, flavonoids, tannins and saponins have been reported in literature. Chemicals screening of both the leaves and the fruits showed the presence of pyrrolizidine alkaloids, coumarins, flavonoids, saponins, terpenes and sterols. The fruit contains about 70% pulp. The pulp contains 6 gm water, 35 gm protein, 37 gm fat, and 18 gm carbohydrate per 100 gm. The seed contains per 100 gm: water 32 gm, fat 46 gm, the principle fatty acids are: palmitic acid, stearic acid and linoleic acid [9-11].

**MATERIAL AND METHODS**

**Plant Material:** Seeds of *Cordia dichotoma* were collected from the farm at Buldhana (Maharashtra, India) in the month of June-July, 2015. The plant was identified by Biotechnology Department, Sant Gadgebaba Amaravati University.

![Fig1.Cordia dichotoma unripe fruits](image-url)
CORDIA DICHOTOMA PHARMACOLOGICAL PROPERTIES

1. **Leaves** – Leaves juice used to control pests and diseases.

2. **Bark** - Decoction is used to treat dyspepsia. The powdered bark is applied to mouth ulcers. The bark is also used to treat fever, abscesses, and tumors. It is mixed with pomegranate rind to treat dysentery. The extract of the bark mixed with coconut water relieves severe colic. Also shows a diuretic and a laxative action.

3. **Fruits Mucilage** - The mucilage of the fruit treats coughs and other chest complaints. It is also used to treat uterus and urethra disorders. The kernel of the fruits in powder form is mixed with oil to heal tinea.

4. **Antidiabetic activity** - Antihyperglycemic effects of *Cordia dichotoma* in the glucose-induced hyperglycemia.

5. **Seeds and leaves extract** - Used to treat degenerative disorders.

6. **Leaves extract** - Shows Antimicrobial activity.

7. **Methanolic extract of Cordia dichotoma** - Hepatoprotective action in male Wistar rats with carbon tetrachloride induced heart damage.

8. **Fruit extract** - Wound healing activity, as cooling, astringent, emollient, expectorant, anthelmintic, purgative, and diuretic.


10. **Fruits** - Antioxidant activity.
11. Flavonoids in all three extracts of CD - showed significant anti-ulcer and cytoprotective.
12. Seeds of Cordia dichotoma - used as anthelmintic, astringent, diuretic, purgative, expectorant and having much more medicinal properties.
13. The fruits of the plant - used a number of pharmacological properties such as analgesic, Anti-inflammatory and hepatoprotective have been reported.\textsuperscript{10,11,12}

CORDIA DICHTOMA

Extraction procedure:
The seeds of Cordia dichotoma was collected carefully washed and dried under shade for 24 h, and then further dried in oven at 30-40°C. Size was reduced with the help of grinder. Powdered seeds were passed through sieve no. #22 and then used for further evaluation.\textsuperscript{10,11}

Extraction of mucilage includes 3 steps.

Step 1: Extraction of mucilage:-
Powdered seeds of Cordia dichotoma were used for the extraction of mucilage. The powdered seeds were added in 1000ml beaker containing 500ml of distilled water, and allowed it to boil for at least 3-4 h with continuous stirring and heating at 60°C for sufficient release of mucilage in water. Concentrated solution was then filtered through muslin cloth in order to separate marc from the filtrate and refrigerated for cooling (3-4°C).\textsuperscript{10,11}

Step 2: Isolation of mucilage:-
To the extract, equal quantity of ethyl alcohol was added for precipitation of mucilage to occur. The precipitated mucilage was washed with ethyl alcohol and then collected through filtration by muslin cloth. Mucilage was further dried in hot air oven at a temperature less than 40°C. The obtained dried mucilage was grinded and passed through sieve #22 and finally stored in air tight container.\textsuperscript{10,11}

ADVANTAGES

- Biodegradable - The naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and they have no adverse impact on humans or environmental health (e.g. skin and eye irritation).
- Biocompatible and non-toxic - Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharides) units. Hence, they are non-toxic.
- Low cost - It is always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. India and many developing countries are dependent on agriculture.
• **Environmental-friendly processing** - Gums and mucilages from different sources are easily collected indifferent seasons in large quantities due to the simple production processes involved.

• **Local availability (especially in developing countries)** - In developing countries, governments promotethe production of plant like guar gum and tragacanth because of the wide applications in a variety of industries.\(^{10,11,12}\)

### DISADVANTAGES

• **Microbial contamination** - The equilibrium moisture content present in the gums and mucilages is normally 10% or more and, structurally, they are carbohydrates and, during production, they are exposed to the external environment and, so there is a chance of microbial contamination. However, this can be prevented by proper handling and the use of preservatives.

• **Batch to batch variation** - Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, while the production of gums and mucilages is dependent on environmental and seasonal factors.

• **Uncontrolled rate of hydration** - Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary. There is a need to develop suitable monographs on available gums and mucilages.

• **Reduced viscosity on storage** - Normally, when gums and mucilages come into contact with water there is an increase in the viscosity of the formulations. Due to the complex nature of gums and mucilages (monosaccharides to polysaccharides and their derivatives), it has been found that after storage there is reduced in viscosity.\(^{10,11,12}\)

### Disadvantages of synthetic polymers in pharmaceutical Sciences

• The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, and poor patient compliance.

• Acute and chronic adverse effects (skin and eye irritation) have been observed in workers handling the related substances methyl methacrylate and poly-(methyl methacrylate) (PMMA). Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site produced by povidone. There is also evidence that povidone may accumulate in organs following intramuscular injections.
• Acute oral toxicity studies in animals have indicated that carbomer-934P has a low oral toxicity at a dose of up to 8 g/kg. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. So, gloves, eye protection and dust respirator are recommended during handling.

• Studies in rats have shown that 5% polyvinyl alcohol aqueous solution injected subcutaneously can cause anemia and can infiltrate various organs and tissues.

• Some disadvantages of biodegradable polymers used in tissue engineering applications are their poor biocompatibility, release of acidic degradation products, poor processing ability and rapid loss of mechanical properties during degradation. It has been shown that poly glycolides, polylactides and their co-polymers have an acceptable biocompatibility but exhibit systemic or local reactions due to acidic degradation products. An initial mild inflammatory response has been reported when using poly-(propylene fumarate) in rat implant studies[10,12,13]

APPLICATIONS

In Pharmaceutical Industry,

• Thickener.
• Emulsifier.
• Gelling Agent.
• Stabilizer.
• Suspending Agent.
• Binder.
• Film former.
• Granulating Agent.
• Disintegrating Agent
• Lubricating Agent.[11,12]

Cordia Dichotoma as Sustained Release Matrix polymer

• Sustained/controlled drug delivery system

Natural polysaccharides and their derivatives are widely explored in the area of sustained /controlled drug delivery systems to improve patient compliance and to provide extended periods of effective blood-levels. In sustained release dosage forms, release of drug is sustained due to the swelling property of these polymers by making a gel-like thick layer which retard the release of drug, hydrophilic or hydrophobic in nature.[19,20,21,22,23,24]
Matrix material

A] An effort has been made to evaluate the efficacy of Cordia gum as a novel sustained release matrix forming material in tablet formulations using diclofenac as model drug. The effect of gum on in vitro drug release profile was examined and compared with a commercially available sustained release diclofenac formulation. It became evident from the study that in vitro dissolution profile of gum formulation was similar to the marketed product. Study suggested that Cordia gum may be a suitable option as an excipient for matrix forming agent to impart enteric resistant and sustained drug delivery in tablet or similar formulation of other drugs too.

B] Polysaccharide mucilage derived from the seeds of Plantago major L. (family Plantaginaceae) was investigated for use in matrix formulations containing propranolol hydrochloride. Cordia dichotoma G. Forst fruit mucilage used as a matrix forming agent in design of sustained release matrix tablets of glimepiride. Propranolol Hcl is a sympatholytic non-selective beta blocker. Propranolol is highly lipophilic and almost completely absorbed after oral administration. Peak plasma concentrations occur about 1 to 4 h after an oral dose. Propranolol hydrochloride is a nonselective beta adrenergic blocking agent, used in the treatment of angina pectoris, hypertension and many other cardiovascular disorders. Propranolol has a short half life (3-4 h) and variable bioavailability due to first pass metabolism.

Mucoadhesive Bilayer patch

In the present research work Cordia dichotoma polysaccharide was used as base matrix polymer for development of mucoadhesive bilayer patch of Ramipril. Because of the properties such as hydrophobicity, low water permeability, drug impermeability, and moderate flexibility, ethyl cellulose was used as a backing layer polymer. In the present study, oral mucoadhesive patch of Ramipril for sublingual and buccal administration was developed and optimized. The efforts were made to improve sublingual and buccal penetration of the drug. Bilayer design of the patch was selected to obtain unidirectional release of the drug, greater surface area of contact, and administer the bitter drug without the taste masking. Ramipril sublingual / buccal patches could be formulated by using solvent evaporation technique using Cordia dichotoma polysaccharide. Mucoadhesive bilayered patches were prepared by using solvent casting method

Transdermal Films
Cordia gum due to its good bioadhesivity may be used in the preparation of transdermal patches. Evaluation of neomycin (0.2% w/v) loaded transdermal films prepared by *Cordia dichotoma* gum (10% w/v) with different percentage of plasticizer and fixed percentage of preservative was carried by comparing the *in vivo* wound healing property with the marketed formulation. It was observed that the *in vivo* wound healing property of transdermal films prepared by *Cordia* gum was similar with marketed product. It suggests that *Cordia dichotoma* gum has enormous potential for use in the preparation and designing of transdermal drug delivery systems. Glycerin, methyl paraben, and drug neomycin in the thickness of the film increases the tensile strength also increases, whereas % water uptake decreases as the thickness increases. The folding endurance and piercing load did not show any trend with increase in the film thickness. It shows the similar effect as that of marketed products. It suggests that *Cordia dichotoma* gum has enormous potential for use in the preparation and designing of transdermal drug delivery systems.[11,12,26,27,28]

- **Microparticulate drug delivery**

Cordia gum also used for the preparation of microspheres because it shows good adhesive property as it is an unnatural polymer, so it shows biodegradation property after drug release. Study ensured the suitability of gum *Cordia* as a potential excipient for sustained release applications.[13,14,15] In a patent claim the method is described for preparation of *Cordia* gum microcapsules using surface polymerization technique. The patent explains the formulation of microcapsules, prepared using 0.5% w/v chitosan (in 5%, v/v acetic acid) and *Cordia* gum: drug (0.03: 1%, w/w). Prepared microparticles have shown good release characteristics. In another study, sustained release Metformin-loaded gum *Cordia/Gellan* beads were prepared employing ionic-gelation technique and optimized using response surface methodology. The optimized bead formulation had adequate % entrapment and more than 80% release in 24 h, which were close to the predicted values. Study ensured the suitability of gum *Cordia* as a potential excipient for sustained release applications.[46,47,48,50,51]

- **Nanoparticles**

An investigation was made to evaluate and optimize the preparation of a novel polymer-surfactant nanoparticles (using *Cordia* gum as the polymer) for ophthalmic delivery of fluconazole using response surface methodology. A w/o/w emulsion containing fluconazole and *Cordia* gum in aqueous phase, methylene chloride as the oily phase, and di-octyl sodium sulfosuccinate and polyvinyl alcohol as the primary and secondary emulsifiers was cross-linked by ionic gelation technique to produce fluconazole-loaded nanoreservoir system.
Comparison of the in vitro release profile of optimized nanosuspension formulation with commercial formulation provides comparable corneal permeability of fluconazole across isolated goat cornea, indicating suitability of Cordia gum based nanosuspension formulation in ophthalmic delivery of fluconazole.[13,14,15,64,36,37,54]

- Emulsifier

Effort was made to investigate the efficacy of Cordia gum as pharmaceutical excipient, in particular as an emulsifier. For this study, castor oil was taken as a model drug and emulsified with Cordia gum. The comparative stability studies were done with that of the emulsion prepared by taking gum acacia as standard emulsifying agent. It was found that the emulsion prepared with 1.5 %w/v of Cordia gum was far more stable and effective compared to emulsion prepared using 10 %w/v of gum acacia. Thus Cordia gum will be a good option as bio-degradable, cheap, economic and easily available emulsifier in the list of pharmaceutical excipient.[30,31,32,33]

- Tablet binder

Natural gums and polysaccharides attracted researchers for many years due to their utility in formulation of solid dosage forms. Narkhede & coworker (2010 & 2011) carried a study to compare the binding effects of isolated Cordia dichotoma mucilage with starch. Mucilage of varying concentrations (8, 10 and 12% w/w) was used to produce aceclofenac tablets by wet granulation method. An increase in gum (binder) concentration led to decrease in friability and increase in disintegration time of the tablets. The results indicate that binding property of gum obtained from Cordia dichotoma (10%w/w) fruit was comparable to starch, hence Cordia gum possess greater potentiality to become the new source of binder and should be exploited for the commercial production of gum. In another study, the fenugreek starch with Cordia gum was compared with gelatin as tablet binder for paracetamol tablets. The Cordia gum exhibited a comparatively higher solubility than fenugreek starch powder and gelatin in cold water. Fenugreek starch with Cordia gum possessed better flow properties than gelatin. The result indicates that in all binder concentrations, comparatively, gelatin showed a faster release of paracetamol than the fenugreek starch and Cordia gum combination of equal concentration. Thus in future fenugreek starch and Cordia gum could compete favorably with gelatin as binder in tablet formulations.[11,12,34,35,36,37]

CONCLUSION

Natural polymers like cordia dichotoma play an important role in the sustained or control drug delivery and it should be safe regarding its toxicity and compatibility. It should be a
good substitute for the synthetic polymers while natural gums are promising biodegradable polymeric materials. However, there is a need to develop natural sources as well as modifying existing natural materials for the formulation of novel drug delivery systems, biotechnological applications and other delivery systems.

REFERENCES

1. Rangari V.D. Pharmacognocy and Phytochemistry. 2nd Ed, Published by career publication, 1:190, 198, 191, 194, 193, 195.
29. American society of Health system Pharmacists (Drug Information, 7272Wisconsin Avenue, Bethesda, , MD 20814, Inc. AHFS ,2004;1869-75.