Review Article

Applications of Tamarind seeds Polysaccharide-based copolymers in Controlled Drug Delivery: An overview

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Abstract

Natural excipient such as gums and mucilage are usually used to formulate different dosage forms as novel drug delivery system. In the present review, we have discussed tamarind naturally derived polysaccharide used as a potential candidate for novel drug delivery system. Natural polymers have advantages over synthetic ones; such as they are chemically harmless, less costly, biodegradable and commonly available. Hydrophilic matrices involving natural polysaccharides are an interesting option for developing sustained release formulations. The utility of TSP and modified TSP as an excipient in novel drug delivery systems is the main focus of this review.

Keywords: Tamarind Seed Polysaccharide (TSP), Carboxymethyl -TSP, Grafting, Thiolated–TSP

Introduction

Polysaccharides are the polymers of monosaccharides. It is obtained from various natural sources such as plant source (e.g. pectin and guar gum), microbial source (e.g. alginate, dextran and xanthan gum), and animal source (chitosan and chondroitin). Polysaccharides have a variety of reactive groups, a wide range of molecular weight, and complex chemical composition, which contribute to diversity in their property (Khanna et al., 1987). Due to the presence of different derivable groups on molecular chains, polysaccharides can easily be modified chemically and biochemically, in various polysaccharide derivatives (Prabaharan et al., 2008). In the recent years, significant attention has been focused for the development of controlled drug formulations to increase patient compliance, specially associated these drugs such NSAIDs, anti-hypertensive, anti-asthmatic and antipyretic drugs. Polymers are used to control the release rate of drugs from different dosage forms. An ideal sustained release matrix formulation should control the release of drug as long as possible, and follow zero order kinetics drug release profile. Natural polysaccharides can be used as an alternative for the hydrophilic polymers. They are biodegradable, nontoxic and biocompatible in nature and swell when comes in contact with the water so they have been used in the formulation of sustained release or controlled release dosage form. Cellulose ethers, xanthan gum, locust bean gum and guar gum are some example of natural polysaccharides Tamarind gum that is obtained from tamarind seeds is another natural polysaccharide which has great potential to use as hydrophilic polymer in controlled drug delivery system. It has been used as gelling, thickening, suspending and emulsifying agents in various dosage formulations (Nandi et al., 1975; Rao et al., 1993; Rao et al., 1946). It has high viscosity, broad pH tolerance, no carcinogenicity, mucoadhesive nature, and biocompatibility. It is used as stabilizer, thickener, gelling agent and binder in food and pharmaceutical industries. The TSP constitutes about 65% of the tamarind seed components (Rao et al., 1993; De freitas et al 2014).

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History

Tamarind usually known as Imli. Tamarind kernel powder came into Indian textile market as a substitute for starch in cotton sizing. (Gerard et al., 1980). Isolation and extraction method of TSP was first devised in the laboratory (Rao et al., 1946), and additionally modified by (Nandi et al. 1975) on a laboratory scale. TSP has the capability to form gels in the presence of sugar or alcohol and can be used to form pectins like gels in jams, jellies and other preserves. TSP was tested and found to be free from carcinogenicity in mice (Sano et al., 1996).

Origin

Tamarind is very common and commercially significant

large evergreen tree that is grown abundantly in the waterless tracks of Central and South Indian states, and also in other South East Asian countries (Glicksman et al., 1996). Tamarind seed gum is obtained from the kernel of the seeds powder. In Asian countries (Shankracharyan et al., 1998), especially in India, tamarind is mainly cultivated and used as an acidifying agent (Kulkarni et al., 2005). Tamarind gum with xanthan gum and hydroxypropyl cellulose, has been used for nasal mucoadhesion studies in powder formulation (Nakamura et al., 1996, Datta et al., 2006). Tamarind gum is also used in the formulation of bioadhesive tablet (Takahashi et al., 2007).

Tamarind seed polysaccharides

Various studies have been conducted on the buccal delivery of drugs using mucoadhesive polymers primarily polysaccharides (Bottari et al., 1975). Polysaccharides are relatively complex carbohydrates. They provide good mechanical properties for application as fibers, films, adhesives, rheology modifiers, hydrogels, emulsifiers and drug delivery agents. For instance, some polysaccharides have proven to improve the contact between drug and human mucosa due to their high mucoadhesive properties (Nakamura et al., 1996, Jangdey et al., 2016). Although tamarind seed polysaccharide (TSP) is used as a constituent in food materials, it has not been extensively evaluated till date for its effectiveness in pharmaceuticals formulations. TSP is a galactoxyloglucan isolated from seed kernel of Tamarindus indica. It possesses property like high viscosity, broad pH tolerance, adhesiveness (Rao et al., 1946) high drug holding capacity, (Kulkarni et al., 1997) and high thermal stability (Saettone et al., 1997). These properties led to its application as a stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. In addition to these, other important property of TSP has been recognized recently is non-carcinogenicity property (Khullar et al., 1998). The Gelling properties of g-TKP/PMA have been studied by determining the rheological parameters. The effect of monomer/catalyst concentrations as well as temperature on the polymerization reaction has been studied as well, the pH-responsive nature of the copolymer exhibit selectivity towards toxic cationic as well as anionic dyes with excellent adsorption capacity (Mishra et al., 2012; Yolanda et al., 2016). Effect of heating conditions on the physical properties of tamarind seed polysaccharide, has been studied, and discovered that the thermally treated tamarind seed polysaccharide can be used as a pharmaceutical excipient (Katiyar et al., 2015).

Chemical Structure

Chemically, tamarind kernel powder is an extremely branched carbohydrate polymer. TSP is a polymer with a molecular weight of 52350 Daltons and a monomer of mainly three sugars-glucose, galactose and xylose in a molar ratio of 3:2:1. A polymer consists of the cellulose-type spine which carries xylose and galactoxylose substituents. The precise sequential distribution of branches is not known. TSP is a branched polysaccharide with a major chain of Â-D-1-glucopyranosyl units, with a side chain consisting of the single D-xylopyranosyl unit attached to every 2nd, 3rd and 4th D glucopyranosyl unit through 1-6 linkage as in Figure 1 (Rao et al., 1993).

Methods of Isolation and Extraction of TSP

Large scale

Method 1

The coat of tamarind seeds removed and obtains the white part of seeds. Coarse powder of tamarind seed prepared by grinder, and then left for 24 h in distilled water. Gum of TSG release, isolation of TSG by muslin cloth. The marc is removing from the gum and equivalent quantity of absolute ethyl alcohol is added to the gum, precipitate formed which is separate by filtration. The isolation is continuous until the material is free of gum. The separated gum is dried in hot air oven at temperature 40ºC. Then the dried gum powdered and stored in airtight containers at room temperature (Malviya et al., 2010).

Method 2

Take 20g of tamarind kernel powder, 200ml of cold distilled water is added and slurry formed. The slurry is poured into 800ml of boiling distilled water. The solution is boiled for 20 minutes under a continuous stirring condition in a water bath. The consequential thin clear solution is kept overnight so that most of the proteins and fibers settled out. The solution is then centrifuged at 5000 rpm for 20 minutes. The supernatant is separated and poured into double the volume of absolute ethanol by continuous stirring. The product was pressed between felt. The precipitate is washed with following solvents absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60° C under vacuum (Khullar et al., 1998).

Method 3

Tamarind kernel powder (TKP) was defatted, and after the powder is further grounded by using Hammer mill or Pin mill that will reduce the size of the powder below 100 mm. The characterization and standardization of gums and mucilage are initially achieved by only a multiple-technique approach. Standard preparations need to be developed to improve quality, efficacy, and effectiveness of the traditional drugs (Nayak et al., 2015).

General properties for tamarind seed polysaccharide

Purified TSP is a high-molecular-weight, polysaccharide

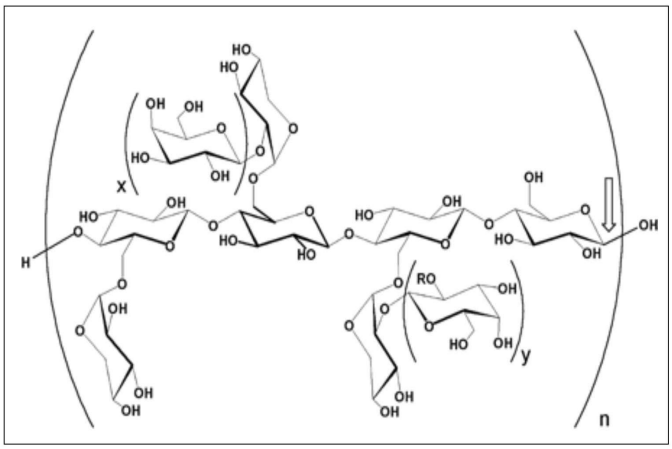

Figure 1. Chemical structure of TSP

consist of cellulose like a backbone that carries xylose and galctoxylose substances (Malviya et al., 2010). It is insoluble in organic solvents and dispersible in warm water to form a highly viscous gel as a mucilaginous solution with a broad pH tolerance and adhesivity (Sahoo et al., 2010). In addition, it is non-toxic and non-irritant with a hemostatic activity. It is a galactoxyloglucan, belongs to the xyloglucan family, and possesses properties such as non-Newtonian rheological behavior, mucomimetic, mucoadhesive and pseudoplastic properties (Kumar et al., 2011).

Tamarind Seed Polysaccharide (TSP) is a galactoxyloglucan (a monomer of mainly three sugars- galactose, xylose, and glucose- in a molar ratio of 1:2:3), which could be safely used for controlled drug delivery systems (Sahoo et al 2010; Rao et al., 1946; Sumathi et al., 2002). It was concluded that increasing the amount of TSP decreases the release rate. As TSP showed a controlled release of both water-soluble and water-insoluble types of drugs (Sumathi et al., 2003), thus when evaluated for tablets it showed slow drug release over 24 h. (Kumar et al., 2011), again observed the sustained release kinetics of both water-soluble and water-insoluble drugs using TSP. Water insoluble drugs like indomethacin showed zero order release from TSP. The extent and amount of release of water-soluble drugs such as acetaminophen, caffeine, theophylline and salicylic acid can be controlled by partially crosslinking the matrix at various degrees of cross-linking (Rajesh et al., 2009). Observed the cumulative release of Paclitaxel at various pH from TSP matrix and found that at increased pH accelerated drug release occurs due to weakened facilitated swelling. This follows that drug release from matrices occurs after water penetration in the matrix, followed by hydration. It then swells and the dissolved drug (polymer hydro fusion) either diffuses out of the matrix and/or erodes out of the gelatinous layer (Malviya et al., 2010). It was found from the study that optimized ratio of drug and polymer served to the optimized oral sustained release Diclofenac sodium from matrix tablet (Sumathi et al., 2003). Used as a carrier polysaccharide for caffeine tablets formulation.

Tamarind Seed Polysaccharides release rate

The release rate of the drug from natural polymers depends upon several factors such as the physicochemical properties of drugs and the polymers, biodegradation rate of polymers, morphology and size of the particles, thermodynamic compatibility exist between the polymers and the drugs (Cicek et al., 1995; Zhang et al., 2002; Abraham et al., 2003) and the shape of the delivery devices (Calandrelli et al., 2002). The preparation, characterization, in vitro swelling and in vitro drug release of metformin HCl-loaded tamarind seed polysaccharide (TSP)-alginate beads were prepared by ionotropic-gelation technique and using $CaCl_2$ as cross-linker (Nayak et al., 2014). Polysaccharide hydrogel was used as release modifier (Kulkarni et al., 2005). This study confirmed that the cross-linked TSP can be used as an effective release retardant and can be successfully used in commercial products (Deveswaran et al., 2009).

Application of derived Tamarind Seed Polysaccharide

Carboxymethylation

Carboxymethylation of tamarind kernel powder TSP has been prepared with monochloroacetic acid in the presence of alkali as a catalyst under heterogeneous conditions. The paste quality and microbial resistance of CM-TSP was much better than that of natural gum. The viscosity of CMTSP in 2% solutions was superior compared to normal gum. Rheological studies showed the non-Newtonian pseudoplastic nature of CM-TSP solutions (Goyal et al., 2007).

Degalactosylation

The aggregation of xyloglucan is the key factor for gel formation and it is unaffected during the enzymatic treatment (Rilton et al., 2011).

Calcium Pectination

The optimized calcium pectinate-TSP mucoadhesive beads containing metformin HCl swell, slowly in the stomach and accordingly adhered to the stomach mucosa allowing more drug to be absorbed minimize the diffusion barriers to increase the absorption period by prolonging the gastric residence time. Therefore newly developed calcium pectinate-TSP mucoadhesive beads containing metformin HCl could possibly be lucrative in terms of prolonged systemic absorption of metformin HCl maintaining tight blood glucose level and advanced patient compliance (Nayak et al., 2014).

Grafting using ethyl acrylate

The synthetic monomer and TSP as the natural polymer has

been taken in a mass concentration ratio of 70:30. A synthesis was conducted in solution with azobisisobutyronitrile (AIBN) as the initiator. Prior to polymerization, nitrogen was bubbled through the reaction mixture to remove any dissolved oxygen. Ethyl acrylate was successfully grafted onto tamarind kernel powder via free radical polymerization. The mechanical properties of this new copolymer recline between those of the two parent polymers, though its tensile strain increased, compared to that of the pure tamarind kernel powder films. It was an environmentally friendly copolymer (Real et al., 2015).

Grafting using methyl methacrylate

Xyloglucan has been isolated from tamarind seed mucilage by aqueous extraction. Grafting of MMA was initiated by the ceric ion in an aqueous medium under N2 atmosphere and the progress of the reaction was monitor gravimetrically by varying different reaction parameters.This material might find potential to be used in drug delivery systems. Grafting material might find potential to be used in drug delivery systems (Mishra et al., 2012). By combining oxidation via galactose oxidase with an indium-mediated allylation reaction the galactose units has been selectively modified by allyl halides. The reaction was carried out by with water as the only solvent, thus the polysaccharide was functionalized in a one-pot reaction. Reactivity with xyloglucan polysaccharides was observed that xyloglucan reacted completely with allyl bromide (Leppänena et al., 2014).

Thiolation

By combining oxidation via galactose oxidase with an indium-mediated allylation reaction the galactose units has been selectively modified by allyl halides. The reaction was carried out by with water as the only solvent, thus the polysaccharide was functionalized in a one-pot reaction. Reactivity with xyloglucan polysaccharides was observed that xyloglucan reacted completely with allyl bromide (Mahajan et al., 2013).

Sulphonation

Sulphated tamarind seed polysaccharide derivatives have been prepared by swelling the polysaccharide in dimethylformamide (DMF) and treating with sulphur trioxide-pyridine complex in DMF at 50°C. The method thorough below was chosen following experimentation to

optimise exposure of the polysaccharide chains to the sulphating reagent and to minimise chain degradation: the high molecular weight products with a reasonably regular distribution of sulphate groups along the chains. Products were analyzed by potentiometric titration as described above and elsewhere in order to determine the degree of sulphation, and by IR and NMR spectroscopy (Lang et al., 1993).

Alkylamination

Oxidation of galactosyl hydroxyl methyl groups to formyl groups, with galactose oxidase catalase as described above for carboxylate derivatives, a reductive amination reaction can be used to introduce alkylamine substituents on C-6 of galactose residues. Ethylamino-, octylamino and nonylamino- derivatives were prepared by addition of a tenfold molar excess of the appropriate alkylamine to the product of galactose oxidase catalase reaction developed (Sumathi et al., 2002).

Crosslinking with Epichlorohydrin

TSP can be cross-linked with epichlorohydrin. The cross-linked TSP exhibits superior wicking and swelling action and hence can be used as a super functional disintegrant. Cross-linked TSP was found to be more effective in retarding the drug release compared to TSP without cross-linking (Kulkarni et al., 1998).

Others applications of Tamarind Polysaccharide Derivatives

TSP is an interesting candidate for pharmaceutical use. It is used as a carrier for a variety of drugs to controlled release. This makes promising excipient for the pharmaceutical industry for the present and future applications.

A. Binder in tablet dosage form

TSP used as a binder for tablet dosage forms, prepared by wet granulation as well as direct compression methods. The results indicated that TSP could be used as a binder for wet granulation and direct compression tablet methods (Kulkarni et al., 1997). It has been observed that the rate of release of the enclosed drug from the matrix is low in acidic Environment and is much higher in the neutral and alkaline environment, reported TSP could be used as a potential candidate for lower gastrointestinal tract targeted drug delivery (Ghosha et al., 2013).

A better-sustained drug release was obtained with the matrix tablet of the tamarind gum. Results showed that the drug release from matrix tablets prepared by using natural polymers can be sustained for more than 12 hrs and the drug release vary with concentration of polymer in matrix tablets (Malviya et al., 2010). Modification of TSP, cassia tora gum and guar gum were investigated by (Sharma et al., 2007; Jana et al., 2016). The main advantage of these grafted gums is that the resultant molecule can be designed to yield a compound with the desired drug release profile. The anti-inflammatory activity of drug-loaded biocomposites lasted over 7 h in albino rats, thus they suggested it can be used as an anti-inflammatory therapeutics carriers (Jana et al., 2016).

B. As a mucoadhesive polymer

TSP is used for the production of thickened ophthalmic

solutions having a pseudoplastic rheological behavior and mucoadhesive properties. The solution is used as artificial tear and as a vehicle for sustained release ophthalmic drugs. TSP have an adhesive nature, thereby prolongs the retention time of formulation onto the surface of eye, unlike other eye preparations. It also increases the resident time of the drug to the cornea, e.g. timolol. Formulated and characterize thiolated xyloglucan polysaccharide nanoparticles (TH-NPs) of acyclovir and studied in a rat model proved that relative bioavailability of acyclovir TH-NPs is ~ 2.575 fold greater than that of the marketed acyclovir drug suspension (Madgulkar et al., 2016). As a mucoadhesive sustained release tablet successfully developed for Nifedipine (Patel et. al 2009) and prepared buccal patches of metronidazol (Jana et al. 2010).

C. In sustained drug delivery

It is a potential polysaccharide having high drug holding capacity which sustained the release of Verapamil hydrochloride. The release pattern was found to be comparable with matrices of other polysaccharide polymers such as ethyl cellulose, hydroxyethyl cellulose, and hydroxypropylmethylcellulose, as well as the commercially available, sustained release tablets (Kulkarni et al., 1997). Sustained release behaviors of both water-soluble drugs (acetaminophen, caffeine, theophylline and salicylic acid), and water-insoluble (Indomethacin) drugs on TSP has been examined. Studies showed that TSP could be used in the formulation of controlled release, for water-soluble and water-insoluble drugs. Zero-order release can be achieved selecting sparingly soluble drugs such as indomethacin along with TSP. The rate of release can be controlled by using suitable diluents such as lactose and microcrystalline cellulose (Kulkarni et al., 1998). It can be used as a binder as well as a polymer for sustained release formulations of low drug loading like Terbutaline sulphate tablet (Kulkarni et al., 1998). For water-soluble drugs, the release amount can also be controlled by partially cross-linking the matrix. The extent of release can be varied by controlling the degree of cross-linking.

D. In ocular drug delivery

The TSP used for topical administration of antibiotics such Eye drops e.g. delivery of 0.3% rufloxacin in the treatment of experimental *Pseudomonas aeruginosa* and *Staphylococcus aureus* keratitis in rabbits. The polysaccharide drastically increased the intraocular penetration of rufloxacin in both infected and uninfected eyes. These data recommended that TSP prolongs the precorneal residence time of antibiotic and enhances the drug accumulation in the cornea, probably by reducing the washout of topically administered drugs (Ghelardi et al., 2004). The concentrations of TSP preferably employed in ophthalmic preparations for use as artificial tears, i.e. products for replacing and stabilizing the natural tear fluid, particularly indicated for the treatment of dry eye syndrome. Formulated, and evaluate carboxy methyl tamarind in situ gelling-based ophthalmic drug delivery system for dorzolamide hydrochloride to enhance the precorneal retention and to improve the ocular bioavailability (Dasankoppa et al., 2016).

E. In controlled release of spheroids

TSP was used as release modifier for the preparation of diclofenac sodium spheroids using the extrusion-spheronization technique with microcrystalline cellulose as a spheronization enhancer. It was established that release was sustained over a period of 7.5 h (Giriraj et al., 2005). Developed spheroids for sustain drug release and also were found to get better the extent of absorption and bioavailability of drug (e.g. Diclofenac sodium, caffeine, etc.) (Sumathi et al., 2003; Chawananorasest et al., 2016).

F. Colon targeting

Matrix tablets were prepared by wet granulation methods using Ibuprofen as a model drug. In vitro release studies mimicking mouth to colon transit established the ability of TSP to release the drug at pH 6.8. TSP was remarkably degraded in rat colon indicating that TSP can be used as a carrier for colonic drug delivery (Mishra et al., 2007). Formulated and evaluated of prednisolone tablets with bio-degradable natural polysaccharides as a career in colon targeted drug delivery (Raj et al., 2013). Developed and evaluated in-vitro propranol HCL matrix tablet, using Tamarind gum, Chitosan and Okra gum for controlled release colon targeted. Suggested the in vitro release profile of the formulations were fixed with various pharmacokinetic mathematical models and analyzed for release profile. The formulations prepared with Tamarind gum prolonged the release for an extended period of time compared to other polymer-based formulation and showed an excellent compression characteristic (Newton et al., 2015). Prepared modified released tablets containing metronidazole loaded microspheres they discovered that formulations containing tamarind gum in different ratios showed drug release up to 93 to 96% within 11 hours.

G. Bio-adhesive tablet

Tablets prepared, with tamarind gum. They were evaluated as bio-adhesive tablets and, found that the tablets showed longest residence time in the oral cavity as compared to that prepared from xanthan gum and carboxycellulose (Datta et al., 2006).

H. As a suspending agent

It has been used for the formulation of thermodynamically stable suspension. In Formulation of suspension of Nimesulide, TSP is used as a suspending agent. They found

that the TSP powder can be used as an effective suspending agent (Deveswaran et al., 2009).

Future perception

Tamarind gum has wide application in the drug delivery. It was found that polysaccharide can be successfully extracted from tamarind seed using water-based extraction procedure. The extracted polysaccharide can be used as a gelling agent in different pharmaceutical preparations, for controlled release of both water-soluble and water-insoluble types of drugs. The rate of release can be controlled by using suitable diluents like lactose and microcrystalline cellulose. For water-soluble drugs, the release amount can also be controlled by partially cross linking the matrix. The extent of release can be varied by controlling the degree of cross-linking.

Conflicts of interest: Nil

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