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Applications of Gum Karaya in Drug Delivery Systems: A Review on Recent Research

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ABSTRACT

Gums exudates are amongst the oldest natural gums. They are already being used as thickening and stabilizing agents from last 5000 years. The major exudate gum—gum karaya—possess a unique range of functionalities. It has been important items of international trade in the food, pharmaceutical, adhesive, paper, textile, and other industries for centuries. The use of naturally occurring biocompatible polymeric materials has been the focus of recent research activity in the design of dosage forms for oral controlled release administration. This paper reviews the literature on gum karaya and describes the varied applications of the gum in drug delivery systems.

Key-words: *Sterculia*, Karaya Gum, Applications

INTRODUCTION

General introduction

The Joint Expert Committee for Food Additives (JECFA/FAO) defines gum karaya as the dried exudate obtained from *Sterculia urens* Roxd and other related species of *Sterculia* (family Sterculiaceae) or *Cochlospermum gossypium* AP De Candolle or other species of *C kunth* (family Bixaceae) [1]. The only other two acceptable contributing species are *S villosa* and *S setigera*. The gum consists mainly of high-molecular weight acetylated polysaccharides which, on hydrolysis, yield galactose, rhamnose and galacturonic acid together with a small amount of glucuronic acid.

After successful toxicological, teratological and mutagenic tests, gum karaya has been declared as Generally Recognized As Safe (GRAS) by the FDA [1]. A study by Eastwood *et al* has shown that gum karaya is safe for use as a food additive, and this is supported by the observation that

dietary gum karaya is neither digested nor degraded by enteric microflora or absorbed to any significant extent in human beings [2,3]. Taking into account its low levels of consumption, toxicological evidence, non-degradability by gut microflora, non-digestibility and non-absorption to any appreciable extent by man, it was concluded that gum karaya is safe for continued use [4].

Chemistry of gum karaya

The primary structure has been shown to be composed of D-glucuronic acid, Dgalacturonic acid, D-galactose and L-rhamnose, in proportions differing according to the quality, type of gum and origin [5-8].

The chemical composition of gum samples obtained from different *Sterculia* species and from different places of origin was found to be quite similar [9,10]. Commercial gum karaya contains about 13–26% galactose and 15–30% rhamnose, which is considerably higher than the rhamnose content of other commercial exudate gums. However, the protein content of about 1% is lower than that of other exudate gums. Gum karaya contains approximately 40% uronic acid residues and 8% of acetyl groups, from which free acetic acid is released on aging. Due to the presence of these acetyl groups, native gum karaya is insoluble and only swells in water distinguished three fractions in gum karaya, based on their solubility in water. Only 10% of the native gum was solubilized in cold water, increasing to 30% in hot water. After deacetylation with dilute ammonia, 90% of the native gum dissolved in water [11-12].

Properties of gum karaya

Gum karaya is one of the least soluble of the exudates gums. Due to its acid stability, high viscosity, and suspension properties, gum karaya is well suited for stabilizing low pH emulsions, such as sauces and dressings [13]. When dispersed in water, the gum particles do not dissolve but adsorb water and swell extensively to more than 60 times the original volume, producing a viscous colloidal sol. The swelling behavior of gum karaya is caused by the presence of acetyl groups in its structure [12]. Chemical deacetylation through an alkali treatment results in a water-soluble gum. Coarse gum particles give a grainy dispersion, whereas finely powdered gum hydrates more rapidly and gives a homogeneous dispersion.

The viscosity of gum karaya dispersions depends on the grade but normally ranges from 0.12–0.40 Pa s for 0.5% dispersions to 10 Pa s for 3% dispersions [14]. Viscosity stability depends on time of harvest, climate during harvest, storage conditions including temperature/humidity. Storage of dry gum results in a loss of viscosity, which is more pronounced for powdered than crude gum. Viscosities are higher when the gum is dispersed in cold water than in hot water [15]. Boiling of the dispersion results in a permanently reduced viscosity, but heating increases the solubility and allows the preparation of dispersions up to 18%, compared to 4–5% in cold water. A decrease in viscosity is also observed following the addition of strong electrolytes and acid or alkali, but his decrease is smaller when the gum is hydrated prior to pH adjustment [10]. Above pH 8, deacetylation occurs, resulting in an increase in viscosity and degree of ropiness. Because of the high uronic acid content, gum karaya resists hydrolysis in 10% hydrochloric acid solution at room temperature for at least 8 h.

Uses of Gum Karaya [10, 16-20]

Gum Karaya is used extensively in various totally unrelated industries because of the properties such as water absorbing / moisture absorbing, gel and film forming, adhesiveness abilities. It is highly resistance to hydrolysis by mild acids and degradation by most of the microorganisms.

Medicinal

The major use of Gum Karaya is as a bulk laxative in view of its ability to form a mucilaginous gel on contact with water. For their use, the Gum is ground to a granule size of 8-30mesh. These granules have a capacity to absorb and after and swell to 70-100% times their original value. The Gum is neither digested nor absorbed by the body.

Gum Karaya also used for liverticular disease and as laxative. Also used to osmotic aids through gum which is from powder, paste, ring, disk, a sheet board advantageous only the other adhesive plasters and cements specially immediately after post surgical core of skin / sensitive skins or in soothing to skin, less likely to produce softness, darker support microbial growth.

It found that the application of powdered Gum Karaya healed the resistant bed sores in few patients. Gum Karaya powder packed in to open wounds increased the normal granulation tissue and also resulted in good epidermal in growth. Gum Karaya is also used in dentine adhesive, medical adhesive tapes for the treatment of stomatities and also used in preparation of pressure-sensitive masking tapes, medical jellies, pastes.

Cosmetics

The film forming property of Gum Karaya makes it useful in the hair setting preparations of hair dressing lotions and finger wave lotions for the beauty trade.

Food Industry

Gum karaya improves the quality of juice in sugar industry. Gum Karaya serves as an emulsifier and binder during meat processing. In salad dressing industry, Gum Karaya is used as a stabilizer by increasing the water, oil emulsion and thereby preventing or slowing separation. The gum also acts as a stabilizer in Sauces, Condiment Bases, Ketchups, Sweet pickle & liquor by increasing the viscosity. A mixture of karaya and arbic gums gave some good results as an emulsifying agent, Gum Karaya mixture & biscuits improve the appearance, symmetry, grain and tenderness whereas in bread it increases the volume and improves the softness, symmetry, extreme, cream colour, taste, odour.

Other Industrial applications

It deflocculates the fibres and serves as binder for fibres. Use of Gum Karaya results in light weight sheets of improved formation and strength. In leather industry it is employed as an ingredient of dressing compositions and in proportions for accelerating the tannin action weighing compositions. Gum Karaya is also used in the manufacture of collagen fibre material.
Gum Karaya in powder form is used as a binding material in many of the textile industries.

The use of naturally occurring biocompatible polymeric materials has been the focus of recent research activity in the design of dosage forms for oral controlled release administration. This

paper reviews the literature on gum karaya (from *Sterculia urens*) and describes the varied applications of the gum in drug delivery systems.

Applications in drug delivery systems

The use of naturally occurring biocompatible polymeric materials has been the focus of recent research activity in the design of dosage forms for oral controlled release administration. Directly compressed matrices were produced containing karaya gum as a release-controlling agent. These swellable hydrophilic natural gums were used to control the release of varying proportions of two model drugs, caffeine and diclofenac sodium, which have different solubilities in aqueous medium. Gum erosion, hydration and drug release studies were carried out using a dissolution apparatus (basket method) at two agitation speeds. Karaya gum displayed a much lower hydration capacity and a higher rate of erosion, markedly affected by agitation speed. The study concluded that Karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role [21].

HV Gangadharappa *et al* recently developed a single unit gastric floating drug delivery system of verapamil hydrochloride using karaya gum and hydroxypropyl methylcellulose (HPMC) as polymers. The feasibility of karaya gum was used for the rate controlling of drug release in the development of floating drug delivery system, evaluating the prepared dosage forms for its sustained release, in vitro buoyancy, swelling index, drug content, and in vitro drug release. The floating matrix tablets were prepared by direct compression technique using a combination of hydroxyl propyl methyl cellulose (HPMC) and karaya gum as polymers and sodium bicarbonate as generating agent. The prepared floating tablets were evaluated for weight variation test, hardness, thickness, swelling index, in vitro floating capabilities, floating lag time, compatibility studies, and in vitro drug release. This swellable hydrophilic natural karaya gum was used to control the release of drug. The results showed that the optimized formulation F8 containing 23.3% of karaya gum (70 mg) and 13.3% of HPMC (40 mg) had good floating capability, shorter floating lag time, and sustained drug release for the period of 8 h [22].

Rao *et al* in 2009 developed sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. Dissolution data was analyzed by Korsmeyer-Peppas power law expression and modified power law expression. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug up to 12 hrs. Among all the formulations, formulation F16 which contains 20% HPMC K15M and 80% of CG release the drug which follow Zero order kinetics via, swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that Tramadol hydrochloride was stable in the

matrix tablets. The DSC and FTIR study revealed that there was no chemical interaction between drug and excipients [23].

The sustained release matrix tablets of diltiazem hydrochloride (DTZ) was developed by Moin and Shivakumar using natural gums (Locust bean gum (LB) and Karaya gum (K)) as novel Hydrophylic matrix systems compared with the extensively investigated Hydroxypropyl methylcellulose [H]. Matrix tablets of DTZ were prepared with different ratio of drug: polymer (1:1, 1:2, and 1:4 of LB, LBK, LBH and LBKH) by direct compression. The matrix tablets were characterized for their hardness, friability, in vitro release study and percentage assay. Totally 12 different formulation were prepared. The result showed that tablets with only LB gum alone cannot control drug release. K gum has higher drug retarding ability than LB gum. The combination of two natural gums resulted in synergistic interaction resulting in more uniform release which could be successfully employed for formulating sustained-release matrix tablets [24].

Natural *agar* and *karaya* gum were modified by Prajapati *et al* using different proportion of distilled water at diverse temperature. The modifications were optimized by a 3^2 full factorial design after microbial growth study as per IP 1996. The modified *agar* (MA) and modified *karaya* gum (MKG) were compared with unmodified agar, karaya gum, starch and Ac-Di-Sol for preliminary evaluations like settling volume, swelling capacity, hydration capacity, moisture content, moisture absorption capacities and for disintegrating behavior in DT formulations using soluble and insoluble drugs with lactose and dicalcium phosphate as diluents. The tablets were also evaluated for in-vitro dissolution test (USP XXIII) and stability study. The result showed that modified agar and karaya gum could be used as super disintegrants in dispersibletablet development as they are easy to prepare, cheap, easily available, biodegradable and stable compared to available synthetic super disintegrants in market [25].

Singh and Pal modified the sterculia gum to develop the novel wounds dressing for the delivery of tetracycline hydrochloride, an antimicrobial agent. This wounds dressing could have the double potential action, first due to inherent antimicrobial nature of the sterculia gum and second due to the controlled release of antimicrobial agent from the hydrogel matrix in the controlled and sustained manner [26].

Singh and Sharma modified the sterculia gum with methacrylic acid (MAAc) to hydrogels for use in drug delivery. The hydrogels were characterized by SEMs, FTIR and swelling studies.The release dynamics of model anti-ulcer drug (ranitidine hydrochloride) from the hydrogels has been studied for the evaluation of the release mechanism. The release of the drug from the hydrogels occurred through non-Fickian diffusion mechanism. Result showed that in the initial stages of drug release from the drug loaded polymers, the rate of release of drug from the polymer matrix has been more than the latter stages. It means after attaining certain concentration the release of drug from polymer matrix has occurred in controlled and sustained manner. It is further concluded that hydrogels developed from the modification of sterculia gum have potential to act as controlled drug delivery devices [27].

In view of the pharmacological importance of sterculia gum and drug delivery devices based on hydrogels, they also synthesized sterculia gum and poly (AAm) based hydrogels by using N,N'-

MBAAm as crosslinker and ammonium persulfate as initiator. The polymeric networks were characterized by SEMs, FTIR and swelling studies. The release dynamics of model anti-ulcer drug (ranitidine hydrochloride) from the hydrogels has been studied for the evaluation of the release mechanism and diffusion coefficients [28].

The gastro-retentive floating drug delivery system has been developed by singh *et al* by simultaneously ionotropic gelation of alginate and sterculia gum by using $CaCl_2$ as crosslinker. The beads thus formed have been characterized by scanning electron micrographs (SEMs), electron dispersion X-ray analysis (EDAX), and Fourier transform infrared spectroscopy (FTIR) analysis. It is concluded from the studies that swelling of the beads is affected by the reaction parameters such as concentration of the sterculia, alginate and crosslinker. Release of drug from beads occurred through Fickian diffusion mechanism. In this mechanism the rate of diffusion of drug molecules from the polymer matrix is much less than that of rate of relaxation of polymeric chains. The higher values have been obtained for average diffusion coefficients than initial and late diffusion coefficients. These values show that rate of diffusion of drug from beads was slow in the initial and later stages of drug release. Further, it is concluded from the foregone discussion that the release of drug from floating beads was less as compared to non-floating beads. At the same time floating nature of beads can make the retention of drug delivery systems in the stomach for longer time and may improve the bioavailability and therapeutic efficacy of the drugs used for the diseases associated with the stomach. Hence these floating beads may be used as gastro-retentive floating drug delivery system for the delivery of anti-ulcer drug [29].

Glipizide microcapsules with a coat consisting of alginate and gum karaya were prepared by Rama Krishna *et al* employing ionic gelation process and emulsification ionotropic gelation process. The microcapsules were evaluated for flow properties, Carr's index, hausner ratio, microencapsulation efficiency, drug release characteristics, surface characteristics; compatibility studies mucoadhesive properties and *in-vivo* hypoglycemic activity. Among the two methods emulsification ionotropic gelation method was found to be more suitable for slow and complete release of glipizide over a long period of time. These microcapsules exhibited good mucoadhesive property in the *in-vitro* wash-off test. In vivo testing into rabbits demonstrated significant hypoglycemic effect of glipizide [30].

Deshmukh *et al* designed oral sustained drug delivery system for freely water-soluble drug, metoprolol succinate using hydrophilic gums *viz.* karaya gum, guar gum and their combination. The present study shows that the single hydrophilic gum like karaya gum and guar gum showed the sustained release profile for short time where as the combination of these two hydrophilic gums in proportion of 6:4 gives sustained drug release for 12 hours [31].

Amoxicillin trihydrate and lidocaine hydrochloride were used as model drugs for Dental molds were prepared using corn zein, carbopol 934 P, gum karaya powder, and poloxamer 407 by mixing and solvent evaporation technique by Ghosh *et al*. In vitro drug-release studies revealed that sustained-release patterns of the drugs in simulated saliva at least for 24 h. The stability study also showed that the drugs were stable in the formulation [32].

The swelling, erosion and solvent front penetration properties of mini-matrices containing xanthan (X), locust bean (LB) and karaya (K) gums were examined & analysed by Sujja-

areevatha *et al* and related to the overall in vitro release kinetics of diclofenac sodium, used as a model drug. Karaya gum with its very slow erosion rate and moderate swellability provides the lowest rate of drug release [33].

Chivate *et al* evaluated *Sterculia foetida* gum as a hydrophilic matrix polymer for controlled release preparation. For evaluation as a matrix polymer; characterization of Sterculia foetida gum was done. Viscosity, pH, scanning electron micrographs were determined. Tablets prepared with *Sterculia foetida* gum were compared with tablets prepared with Hydroxymethylcellulose K15M. The in vitro release profiles indicated that tablets prepared from *Sterculia foetida* gum had higher retarding capacity than tablets prepared with Hydroxymethylcellulose K15M prepared tablets. The differential scanning calorimetry results indicated that there are no interactions of *Sterculia foetida* gum with diltiazem hydrochloride. It was observed that release of the drug followed through surface erosion and anomalous diffusion. Thus, study concluded that *Sterculia foetida* gum could be used a controlled release matrix polymer [34].

Matrix tablets of phenylpropanolamine were fabricated by Senapati using karaya gum and guar gum, alone or in combination with other excipients. The tablets with karaya gum exhibited greater swelling indices than those with guar gum. Further studies showed that combination of karaya gum and guar gum exhibited more sustained release than individual gum [35].

Singh *et al* developed the floating matrix tablets of metoclopramide hydrochloride (MHCl) for improving its bioavailability by prolonging gastric residence time. Floating matrix tablets (FMT) of MHCl were prepared using the polymers guar gum (GG), karaya gum (KG), HPMC E15 (HE) alone and in combination with HPMC K15M (HK) and gas generating agents such as calcium carbonate and citric acid [36].

Hydrophilic matrices of gum karaya (GK) and guar gum (GG) using theophylline (TH) as a model drug were prepared by Babu *et al* for oral controlled release. In vitro release studies were performed for these matrix systems to find out the suitable drug-carrier ratio, which extend the drug release up to 24 h. Therefore, the present study disclosed that the usage of colon degradable polymer offers an advantage in the design of controlled release dosage forms of drugs, which has good absorption properties throughout the gastrointestinal tract [37].

A soft polymeric mold containing antibiotic and analgesic drugs and having an appropriate consistency to adhere to the tooth, was developed by Mukherjee *et al* for sustained drug release to provide better relief in dental patients. Eudragit L 100-55, carbopol 971 P, gum karaya powder and ethyl cellulose were used to prepare the mold "Denticaps" containing Lidocaine hydrochloride and Amoxicillin trihydrate individually and in combination, by mixing and solvent evaporation technique [38].

Some naturally occurring biocompatible materials were evaluated by Park *et al* as mucoadhesive controlled release excipients for buccal drug delivery. A range of tablets were prepared containing 0-50% w/w xanthan gum, karaya gum, guar gum, and glycol chitosan and were tested for swelling, drug release, and muco adhesion. Karaya gum demonstrated superior adhesion and was able to provide zero-order drug release, but concentrations greater than 50% w/w may be required to provide suitable sustained release [39].

Healthy adult (New Zealand, Dutch Belt, and Wild) rabbits were infected with rabbit papilloma virus (Shope variety). The resultant papillomas were treated with salicylic acid in a new transdermal drug delivery system utilizing a karaya gum glycol matrix by Mottaz *et al*. Biopsy samples of treated papillomas were taken at 1, 2, and 3 weeks after initiation of treatment and examined by electron microscopy. The observed changes during the course of treatment indicated that the karaya gum glycol matrix effectively released salicylic acid into the stratum corneum. Further, the rate of delivery of salicylic acid was such that the desired keratolytic activity was achieved with minimal inflammatory response [40].

A clinical study was conducted by Bart to evaluate the efficacy of a new delivery system for administering salicylic acid for the treatment of *verruca vulgaris.* The study compared wart resolution among volunteers who used karaya gum patches. The cure rate was 69% for warts treated with patches containing salicylic acid, which was significantly higher (p less than 0.01) than for warts treated with control patches (35%) [41].

The use of two recently introduced skin protective preparations in the treatment of perifistular skin inflammation is described by Gross *et al*. Karaya gum in paste form (karaya paste) was used alone or in combination; with drainable collecting appliances. The method protects the inflamed skin from fistula discharge and allows healing to proceed beneath the dressing [42].

A novel matrix system of flurbiprofen as an oral controlled release formulation was prepared by Babu *et al* using gum Karaya as release retardant. Lactose or dicalcium phosphate was incorporated to improve the drug release rate. The study showed that gum karaya matrices containing lactose has satisfactory release characteristics [43].

Raghavendra Rao *et al* developed controlled zero-order release glipizide bilayered matrix tablets using different grades of hydroxy propyl methyl cellulose (HPMC) as novel release modifier along with xanthan gum (XG), guar gum (GG), and karaya gum (KG) as release retardants. The release data were fit into different kinetic models (zero order, first order and Korsemeyer-Peppas powers law equation). it is finally concluded that, the bilayer matrix tablet technology can be successfully applied for achieving ideal zero-order release pattern for glipizide using blend of HPMC K100M, HPMC K15M and ethyl cellulose, xanthan gum, guar gum, karaya gum can be used as rate controlling polymers by appropriate selection of the level of polymers in the matrix tablets [44].

Cox *et al* prepared mini-matrix tablets containing S(+)-ibuprofen, used as a model drug, karaya gum as the hydrophilic matrix to retard drug release. Mini-matrix tablets containing S()-ibuprofen have been prepared by the wet granulation method. The hydrophilic matrix was formed with karaya gum or hydroxymethylcellulose (HPMC) together with a choice of additives from lactose, Encompress®, Avicel® PH101, talc and Lubritab®. Multiple unit dosage forms (MUDFs) were subsequently obtained by encapsulating the mini-matrix tablets into hard gelatin capsules for mini-matrices containing Avicel®, polymer relaxation was dominant throughout the dissolution time period. The release of S(+)-ibuprofen from S(+)- ibuprofen: HPMC: lactose 1:1:1 was slower than karaya gum mini-matrices [45].

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