DEVELOPMENT AND EVALUATION OF MODIFIED NATURAL POLYMER BASED MATRIX TABLETS FOR SUSTAINED RELEASE OF A HIGHLY WATER SOLUBLE DRUG

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Synopsis

Oral delivery is probably the most acceptable and favourable mode of drug delivery. The reason for such popularity is its non-invasiveness, self-administration, and low cost. This leads to high patient acceptability. Approximately 90% of all medications provided for a systemic effect are taken orally. The dosage forms for oral delivery of drugs primarily includes tablets, capsules and various liquid formulations. The tablets dosage form is one of the most preferred dosage form both by physicians and patients. Tablets are unit dosage forms where one unit of the dose is accurately loaded, which minimizes any error of administering the right dose of the drug. The tablet dosage form thus offers the minimum content variability and highest dose accuracy. Additionally, the cost of tablets is the lowest of all solid dosage form, and they are the compact and lightest of all oral dosage forms. Lastly, tablets are the most suited for large scale production with minimum tableting infrastructure among all unit oral forms.

The tablet dosage form when taken orally, first disintegrates to release the granules. The drug from the granules then solubilizes in the gastrointestinal medium, which is then absorbed and the drug reaches in the blood circulation. Since the total amount of drug is exposed in the gastrointestinal medium and is available for absorption, the rate and amount of drug absorption increases exponentially and the blood drug concentration steadily increases with time. As the blood drug concentration attains a certain concentration, the therapeutic onset of drug action takes place. Gradually with time the plasma drug concentration increases to attain the maximum drug plasma concentration. After the maximum plasma concentration, the blood drug concentration starts to decline. So far the drug concentration is above the minimum effective concentration, the therapeutic effect of the drug persists, after which the drug therapeutic effect terminates.

If it is necessary to keep a sustained therapeutic plasma level of drug between the medication intervals, then a greater drug dose has to be dispensed. This higher drug dose may produce inordinately high and often toxic drug levels for significant periods. For attenuating toxic manifestations due to high drug levels, the dose of the drug has to be reduced. This may, on the other hand, produce plasma levels of the drug which for much of the period of treatment will remain below the threshold efficacy. In either case, the fraction of administered dose utilized by the patient is depressingly small amount. Maximum availability of the drug from drug delivery systems utilizing minimum amounts of the drugs can be achieved by repeated administration of small increments of the total dose. However, uninterrupted dispensing of the drugs by conventional delivery systems is both impractical and impossible. Repeated administration of the drug may also be associated with chronic side effects of the drug. The

cost of therapy also escalates and all these factors contribute towards poor patient compliance and acceptability.

Thus, the conventional tablet dosage form has the following limitations. The blood drug concentration (i.e. the site of drug action) varies over subsequent dosing intervals even at the "steady state" situation. It is difficult to sustain a fixed therapeutic drug concentration at plasma for the duration of treatment. The variations in the plasma drug concentrations may result in an under or over medicated patient for periods of time. Frequent dosing for the drugs having shorter biological half-lives are necessary to maintain steady state plasma concentration within the therapeutic limits. For such drugs, maintaining therapeutic plasma concentration is dependent to the consequences of the overnight no dose period and missed doses. The regimens requiring frequent administration of conventional dosage form leads to patient non-compliance. This is an important reason behind therapeutic failure or inefficiency.

The problems associated with the conventional tablet dosage form can be overcome with modified release drug delivery systems. The sustained release form achieves the slow release of the medication over a prolonged duration after administration a single drug dose. The sustained release forms immediately release a drug dose to achieve the minimum plasma therapeutic concentration and then maintain the same for a long duration. The sustained release forms reduce variations of plasma drug levels, frequency of drug administration, adverse effects, and overall therapy cost. All these factors contribute towards enhanced patient conformity and convenience.

Matrix tablets are prominent oral sustained release drug delivery systems because of their high level of reproducibility, simplicity, stability of the dosage forms and easy to scale-up, manufacturing, and process validation. Scientific progress in the field of matrix tablet formulations have made sustained release product formulation easier, simpler, and improved. Matrix technologies are able to deliver a wide range of drugs with divergent biopharmaceutical and physicochemical properties. The basic components of a sustained release matrix tablet include the drug, matrix former (release controlling agent), release modifiers (wicking agents, channelling agents etc), and lubricants and flow aiding agents. The matrix materials or the release controlling agents may be lipid matrices, insoluble polymer matrices, and hydrophilic colloidal matrices.

Polysaccharides are the most widely available polymers and can be obtained from algal, plant and animal sources. Polysaccharides consists of monosaccharide units linked together by glycosidic bonds. They are carbohydrates having great number of sugar molecules covalently interconnected by glycosidic bonds. They can be non-ionic (like tara gum, xanthan gum),

cationic (like chitosan) and can also be anionic (like sodium alginate, pectin). The polysaccharide can also be of plant origin (tara gum), animal origin (chitosan), and algal origin (alginate). Natural polysaccharides have been extensively used to develop sustained release matrix tablets owing to their biocompatibility, easy availability, non-toxicity and wide regulatory acceptance. Different hydrophilic polysaccharides like xanthan gum, guar gum, sodium alginate, gellan gum have been successfully used as matrix materials for sustained delivery of drugs.

Drug dissolution from a natural hydrophilic polysaccharide matrix is generally dictated by the erosion, swelling, and viscous nature of the concerned polysaccharide. Drug solubilization from such matrixes can be tailored by controlling the viscosity, erosion and swelling of the polysaccharide. Crosslinking of the polysaccharide polymeric chains is a simple procedure to control the viscosity, erosion and swelling of the polysaccharide and thus to monitor the drug release from the hydrophilic polysaccharide matrix. Cross-linking can ionic or chemical. Chemical cross-linking of the polysaccharide polymer chains involves the use of harmful chemical reagents like glutaraldehyde, tripolyphosphate, and is thus not recommended. Ionic crosslink can be done under mild aqueous conditions by use of metal cations like Ca^{2+}, Ba^{2+}, Al^{3+}, Fe^{3+}. Ionic crosslink of natural polysaccharide chains is thus advocated.

Natural polysaccharides as matrix materials for sustained delivery of drugs have been extensively exploited. But they suffer from some drawbacks. Natural polysaccharides are prone to microbial contaminations, varying physicochemical properties, batch-to-batch variations and possibility of heavy metal contaminations. More importantly, the aqueous solubility, uncontrolled rate of hydration and swelling, and rapid matrix erosion and degradations inhibit the natural polymers from becoming an effective matrix material.

The polysaccharide polymeric chains have diverse chemical compositions and functional groups which lend themselves for various chemical derivatization. The derivatization of the polysaccharide polymeric chains can bypass the inherent problems of the polysaccharide and opens up for newer avenues of applications. Chemical derivatization of polysaccharides includes phosphorylation, sulfation, thiolation, carboxymethylation etc. Tailor made derivatives of the natural polysaccharides can be synthesised under simple and mild conditions. These tailored derivatives have been utilized in drug delivery and allied fields.

The derivatization of the natural polysaccharides are done to modify the physicochemical, rheological, and biological properties of the polysaccharides, to make them potential candidates as drug delivery carriers. The solubility and viscosity profiles, swelling and erosion

characteristics of the polysaccharides are fine-tuned according to the requirements of the drug delivery carriers by the chemical derivatization process.

Carboxymethylation is one of the most versatile and popular derivatization process. Carboxymethylation is done under mild alkaline aqueous environments and involves the incorporation of o-carboxymethyl groups in the polysaccharide polymeric chains. The hydroxyl groups of the polymers are substituted by the o-carboxymethyl groups during the reaction. Carboxymethylation imparts an anionic nature to the polysaccharide making it amenable to crosslink with divalent and trivalent metal ions and form water insoluble hydrogels, by a process known as ionotropic gelation. Ionotropic cross-linking of the polysaccharide polymeric chains is a suitable procedure for controlling the erosion, swelling, and drug delivery from the polysaccharide hydrogel matrix.

Tara gum (TG) is a seed endosperm galactomannan non-ionic polysaccharide obtained from caesalpinia spinose tree. TG backbone is primarily comprised of a linear main chain of (1–4)-β- d -mannopyranose units joined by (1–6) linkage with α- d -galactopyranose units. TG is a popular stabilizer and thickener in the food industry and is also used as edible films in food packaging industry. Grafted TG based superabsorbent hydrogels have also been synthesized. However, TG is highly hydrophilic and its rheological properties are not suited for the development of sustained release matrices. Carboxymethylation modifies the rheological, physicochemical, hydrophilic and swelling attributes of the natural polysaccharide. With this context, TG was derivatized to carboxymethyl TG (CMTG) by incorporating O-carboxymethyl groups in TG polymeric chains, with an anticipation to introduce ionic nature to TG making it amenable to cross-link with metal ions and also alter its swelling and hydrophilic characteristics.

Tramadol hydrochloride (TH), is a synthesized analgesic having both opioid and non-opioid characteristics. TH mainly works on the CNS. TH was sanctioned by the United States Food and Drug Administration (USFDA) for controlling, treating and mitigating modest to extreme pain in 1955. TH has structural similarities to morphine and codeine, but 10-times and 6000-times less potent than codeine and morphine respectively. It has a half-life of about 5.5 h and oral administration of 50 mg to 100 mg is required every 4-6 h. The daily maximum oral dose of tramadol is 400 mg. To reduce frequency of dosing, dose related side effects, and enhance patient compliance, sustained/controlled release of TH is necessary. Tramadol sustained/controlled release forms are documented in literature. Oral administration of tramadol sustained release tablets attains a bioavailability of 87% - 95%, compared with capsules. Long term treatment with tramadol produces satisfactory osteoarthritic, low back,

and post-operative pain management with minimum side effects and enhanced patient acceptability. Considering all the above factors, formulation of tramadol sustained release hydrogel tablets was undertaken.

Modification of TG to CMTG was performed in an alkaline milieu by reacting TG with MCA. The degree of substitution (DS) of the carboxymethylation reaction was determined. The carboxymethylation reaction was confirmed by ^{13}C solid state NMR and FTIR studies. XRD, DSC analysis of CMTG was performed. The DS of optimized CMTG was 0.84. The ^{13}C spectra of TG displayed three specific absorption signals at δ = 62.10 ppm for C6 carbon of the mannose unit, δ = 72 ppm for merging of signals of mannan carbon atoms at 2, 3, 4, and 5 position, and δ = 101.70 ppm for C1 mannan carbon atom. The solid state ^{13}C spectra of the CMTG revealed three extra signals at δ = 179.1, 169.2, and 167ppm, representing the carbonyl atom of the carboxymethyl groups at 6-O, 3-O, and 2-O positions respectively. The appearance of the three additional signals in the spectra of CMTG confirms the carboxymethyl reaction at all three locations. The IR spectrum of TG showed a wide peak at 3303 cm^{-1} representing the stretching of the OH moieties of the gum. The peak intensity at 3303 cm^{-1} in the IR spectrum of CMTG appears to be of diminished intensity indicating that the OH groups are substituted with the carboxymethyl groups, ascertaining the insertion of the carboxymethyl groups onto TG structure. Moreover, CMTG displayed characteristics absorption peaks at 1591 cm^{-1} signifying the COO^- asymmetric stretching. Spectrums at 1414 cm^{-1} and 1321 cm^{-1} stands for symmetric stretching of COO^-. These peaks were not present in the IR spectrum of TG. The occurrence of the extra new peaks in the spectrum of CMTG indicated that the OH groups of TG are substituted by the carboxymethyl moieties. The XRD trace of TG indicates its amorphous nature. The XRD pattern of CMTG also seems like an amorphous hallow, except the appearance of twin intense peaks of intensities 877cps and 484cps at diffraction 2θ 31.68º and 45.40º respectively. The presence of the two intense peaks in the XRD pattern of CMTG highlighted the slight improvement in crystallinity of TG after the carboxymethylation reaction. The thermogram of TG is characterised by the presence of an expanded endotherm at 69ºC assignable to the loss of water from the polymer sample. An exotherm at 306ºC indicates the thermal decomposition or degradation of the gum. The DSC curve of CMTG displayed an expanded endothermic event between temperature 70ºC and 120ºC. This event represents water loss from CMTG sample. A second exothermic event for CMTG appeared at 259ºC signifying the thermal decomposition or degradation of CMTG. Comparison of the thermal events of the TG and CMTG highlights that the decomposition temperature of CMTG is lower compared to TG.

The synthesised gum was evaluated for sub chronic oral toxicity to gather some knowledge about the health risks that may happen following oral intake of the gum. As per the outcomes of the sub chronic oral toxicity study, it can be concluded that the synthesized CMTG was bereft of any suggestive feature of haematological toxicity, behavioural toxicity, hepatotoxicity and nepherotoxicity in any dose group. Nil lethality in all the dose groups pointed out that the LD_{50} of CMTG is above 2000mg/kg. According to the GHS, if the LD_{50} value is higher than 2000 mg/kg dose, then the sample under investigation will fall under "category 5" and the toxicity will be rated "zero". Therefore, CMTG falls under "category 5" with "zero" toxicity rating.

Following synthesis, optimization and characterisation of CMTG, aluminium and/or calcium cross-linked CMTG hydrogel matrices were developed by wet granulation method. The weight percentage of the aluminium and calcium ions were varied from 0-12% and 0-15% w/w of the matrices respectively. The impact of the cross-linking ions on the erosion, swelling and *in vitro* TH release from the matrices have been explored. Aluminium and calcium cross-linked CMTG matrices swelled immediately to various extents in pH 1.2 acid solution, and subsequently the swelling progressively reduced demonstrating mass loss (erosion) of the matrices. Uncross-linked CMTG matrices swelled 381% after 2 h in pH 1.2 acid solution, thereafter the swelling gradually declined (194% after 8 h). The erosion of uncross-linked CMTG matrices showed an early burst erosion (34% at 2 h), following which the erosion gradually increased with time (69% at 8 h). $AlCl_3$ incorporation in the hydrogel matrices changed the erosion and swelling characteristics of the matrices substantially. Accentuating $AlCl_3$ concentration in the hydrogel matrices from 3-9% w/w declined the erosion and swelling characteristics. But, further elevation in $AlCl_3$ concentration to 12% w/w stimulated the matrix erosion, although the swelling declined. Reduced water intrusion velocity through the thick polymeric or gel-like matrices was the cause of fall in swelling rate of the hydrogel matrices with the rise in $AlCl_3$ concentration. Elevation in the $AlCl_3$ amount in the matrices effected the decline of water intrusion velocity. The stiff hydrogel layer slowed down matrix dissolution and decrease in the percentage erosion of the hydrogel matrices with the rise in the $AlCl_3$ concentration. Like aluminuim ions, calcium ions also changed the erosion, swelling characteristics of the matrices substantially. Elevation in the Ca^{2+} ions concentration in the hydrogel matrices from 3-12% w/w declined the erosion and swelling. But additional rise in the Ca^{2+} ions concentration to 15% w/w escalated the matrix erosion, however the swelling declined. Like Al-CMTG matrices, the water intrusion velocity declined through the calcium cross-linked dense and viscous hydrogel layer, resulting in decline in swelling of the matrices. The fall in erosion was

attributable to the development of firm hydrogel layer with lesser matrix dissolution rate. Calcium and aluminium cross-linked CMTG matrices swelling kinetics followed Fickian diffusional kinetics.

The *in vitro* TH dissolutions from uncross-linked, and aluminium or calcium cross-linked CMTG matrices revealed the significant impact that the cross-linking ions had on the TH release behaviour. Matrices formulated with CMTG only liberated 46% and 96% of TH at 2 h and 8 h respectively. Aluminium ion cross-linking of the CMTG matrices significantly changed the TH dissolution pattern. Increase in $AlCl_3$ concentration in the matrices from 3% w/w to 9% w/w decreased the TH dissolution rate. However, elevation in the $AlCl_3$ amount to 12% w/w increased the TH dissolution rate significantly. The AUCs dropped with the increase in $AlCl_3$ concentration 3%-9% w/w of the matrices, and then again augmented at 12% w/w $AlCl_3$ concentration considerably. The MDT increased with the increase in $AlCl_3$ concentration 3%-9% w/w of the matrices, and then again declined at 12% w/w $AlCl_3$ concentration considerably. The TH dissolution characteristics was simultaneous with erosion, swelling characteristics of the hydrogel matrices. Similar results were observed for calcium cross-linked CMTG matrices. Increase in $CaCl_2$ concentration in the matrices from 3% w/w to 12% w/w decreased the TH dissolution rate. However, elevation in the $CaCl_2$ amount to 15% w/w increased the TH dissolution rate significantly. The AUCs dropped with the increase in $CaCl_2$ concentration 3%-12% w/w of the matrices, and then again augmented at 15% w/w $CaCl_2$ concentration considerably. The MDT increased with the increase in $CaCl_2$ concentration 3%-12% w/w of the matrices, and then again declined at 15% w/w $CaCl_2$ concentration considerably. The TH dissolution characteristics was simultaneous with erosion, swelling characteristics of the hydrogel matrices. Viscosity of solutions mimicking the compositions of different hydrogel matrices was also in accordance with the TH dissolution behaviour. Photographs of hydrogel matrices at different time intervals and SEM microimages of the hydrogel matrices also bolstered the TH dissolution behaviour.

The TH dissolution from optimised single cross-linked hydrogel matrices containing 9% w/w $AlCl_3$ was compared with a marketed commercial tablet TRD-CONTIN® (TH 100 mg). TH dissolution from optimised single cross-linked hydrogel matrices and commercial tablet in pH 1.2 acid media almost overlapped and merged with each other and difference was not significant. However, TH dissolution from optimised single cross-linked hydrogel matrices and marketed commercial tablet in pH 7.4 buffer media was reckoned significant. TH dissolution from optimized optimised single cross-linked hydrogel matrices was more sustained and

slower as compared to marketed tablet in pH 7.4 buffer media. Thus, the developed matrices had a better sustained dissolution pattern as compared to the marketed commercial tablet.

Al-CMTG matrices containing 9% w/w $AlCl_3$ and Ca-CMTG matrices containing 12% w/w $CaCl_2$ gave the most sustained TH dissolution form the matrices. Development of dual cross-linked (containing both Al^{3+} and Ca^{2+}) hydrogel matrices was done at the already optimized concentrations of the cross-linking ions. TH dissolution from CMTG hydrogel matrices cross-linked with different weight ratios of Ca^{2+} and Al^{3+} ions (where the overall cross-linking ion concentrations was maintained at 9% w/w of the matrices) demonstrated that increase in the weight percentage of Ca^{2+} ions in the matrices expedited TH dissolution from the matrices. TH dissolution from CMTG hydrogel matrices cross-linked with different weight ratios of Ca^{2+} and Al^{3+} ions (where the overall cross-linking ion concentrations was maintained at 12% w/w of the matrices) demonstrated that increase in the weight percentage of Al^{3+} ions in the matrices slowed down TH dissolution from the matrices. The dual cross-linked hydrogel matrices where the overall cross-linking ion concentrations was 12% w/w of the matrices, and weight ratio between Al^{3+} and Ca^{2+} ions was 1:1 gave the most sustained TH dissolution releasing 75% TH after 10 h of dissolution.

With the purpose to further prolong TH dissolution from the matrices, TG was incorporated to the optimized dual cross-linked hydrogel matrices. Accordingly, semi-IPN hydrogel matrices of CMTG and TG have been prepared. The erosion, swelling, and TH dissolution from the semi-IPN matrices have been investigated. Keeping all the variables (ratio between Al^{3+}/Ca^{2+} ions and polymer: cross-linker) of the dual cross-linked hydrogel matrices constant, CMTG was progressively substituted with TG in the matrices. Weight percentage of TG was 5% w/w, 10% w/w, 15% w/w, and 20% w/w of the total polymer. Incorporation of TG onto the dual cross-linked matrices produced substantial changes in the in vitro TH dissolution profile. TH dissolution progressively augmented with the elevation in the TG weight percentage in the matrices. MDT and AUCs progressively increased with the elevation in the TG weight percentage in the matrices. This was due to the elevation in the swelling and erosion characteristics of the semi-IPN matrices.

Semi-IPN hydrogel matrices was unable to meet the objective of sustaining TH dissolution. Contrarily, it accelerated TH dissolution. By slightly fabricating the matrix development method, TG was not incorporated inside the granules, but incorporated inside the matrix. In other words, TH and CMTG was triturated with the cross-linking solutions as usual and upon completion of the granulation, TG was added and homogenously blended with the granules and then compressed. In such case, TG was extragranular (outside the granules) such that TG

will form a fine thin coating on the dual cross-linked CMTG granules. Substantial changes in TH dissolution pattern were perceived from semi-IPN extragranular hydrogel matrices. Burst TH dissolution observed with all previously developed hydrogel matrices, is significantly reduced from semi-IPN extragranular hydrogel matrices. Elevation in the extragranular TG quantity in hydrogel matrices 5% w/w, 10% w/w, and 15% w/w significantly declined TH dissolution. However, further increment in the extragranular TG quantity to 20%w/w, significantly expedited TH dissolution. This was due to the formation of thick and highly viscous coating over the TH-rich granules, which hindered TH dissolution from the matrices. However, at an elevated TG concentration (20% w/w), TH dissolution augments. This was due to the imbalance created between the ratio of CMTG and the cross-linking ions and also due to change in the hydrodynamic condition of the matrix. Decline in burst TH dissolution from the semi-IPN extragranular matrices was because the matrices surface was almost devoid of TH and primarily composed of TG. The TH dissolution from matrices obeyed Fickian diffusion (R^2 values 0.922-0.985) with release exponent (n) values less than 0.5.

The pharmacokinetic specifications and plasma drug concentration-time curve following administration of oral TH solution and optimized hydrogel matrices have been investigated. The in vivo pharmacokinetic study demonstrated that the optimized hydrogel matrices produced sustained TH delivery and could decrease the TH dosage frequency.

The accelerated stability study was conducted on the optimized extragranular semi-IPN hydrogel matrices containing 15% w/w of TG in the matrices. The matrices were kept at 40±2°C at RH 75±5% for 3 months. Following the accelerated stability studies, the matrices were checked for its hardness, friability, TH content and in vitro dissolution. Hardness, friability and TH content of the tablets following the stability studies didn’t deviate from the hardness, friability and TH content of the original matrices. The in vitro TH dissolution profiles of the matrices before and after the stability studies were almost same and the dissolution curves almost overlapped and merged. The accelerated stability studies indicted the stability of the developed hydrogel matrices under adverse storage conditions.