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RESEARCH ARTICLE

Development of Metoprolol Tartrate Sustained Release Formulations by using Modified Starches

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ABSTRACT

This study is aimed to design oral sustained-release formulations for the anti-hypertension drug Metoprolol tartrate. This drug exhibits required physicochemical and pharmacokinetic parameters to formulate sustained-release formulations. The literature survey reveals that Sustained Release formulations for some drugs were prepared by employing Modified Starch known as Calcium Starch. Natural Starches such as potato starch, rice starch, and corn starches can be chemically modified using cross-linking agents such as calcium chloride and it may be used as release retardants. The functional characteristics of starch may vary from source to source. Hence, there is a scope to evaluate the effect of starch on release characteristics of the drug. Further, the drug release is expected to be altered by the proportion of release retardant and hence there is a need to optimize the composition by screening the composition. Hence, there is scope for comparative evaluation of modified starches prepared using different naturally occurring starches and their effect on release characteristics of metoprolol tartrate for sustained release formulations.

Keyword: Metoprolol, Starch, Tartrate

INTRODUCTION

Starch is a natural, cheap, available, renewable, and biodegradable polymer produced by many plants as a source of stored energy. It is the second most abundant biomass material in nature. It is found in plant leaves, stems, roots, bulbs, nuts, stalks, crop seeds, and staple crops such as rice, corn, wheat, cassava, and potato. From serving as food for man, starch has been found to be effective in drying up skin lesions (dermatitis), especially where there are watery exudates consequently, starch is a major component of dusting powders, pastes, and ointments meant to provide protective and healing effect on skins. Starch mucilage has also performed emollient and major base in enemas. Because of its ability to form complex with iodine, starch has been used in treating iodine poisoning. Acute diarrhea has also been effectively prevented or treated with starch-based solutions due to the excellent ability of starch to take up water. In pharmacy, starch appears indispensable; it is used as excipients in several medicines. Its traditional role as a disintegrate or diluents is giving way to the more modern role as drug carrier; the therapeutic effect of the starch-adsorbed or starch-encapsulated or starch-conjugated drug largely depends on the type of starch.

Basic structural design of starch

Starch, which is the major dietary source of carbohydrates, is the most abundant storage polysaccharide in plants and occurs as granules in the chloroplast of green leaves and the amyloplast

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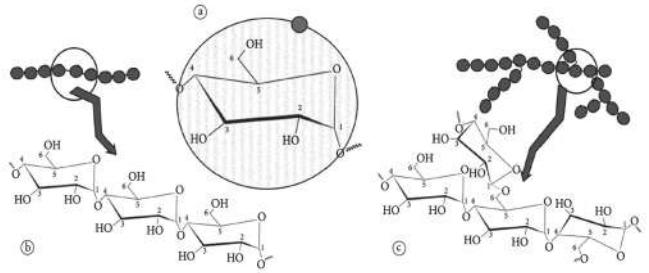
of seeds, pulses, and tubers. Chemically, starches are polysaccharides, composed of a number of monosaccharides or sugar (glucose) molecules linked together with D-(1-4) and/or D-(1-6) linkages. The starch consists of 2 main structural components, amylose, which is essentially a linear polymer in which glucose residues are D-(1-4) linked, typically constituting 15–20% of starch, and amylopectin, which is a larger branched molecule with D-(1-4) and D-(1-6) linkages and is a major component of starch. Amylose is linear or slightly branched, has a degree of polymerization up to 6000, and has a molecular mass of 105–106 g/mol. The chains can easily form single or double helices. Amylopectin on the other hand has a molecular mass of 107–109 g/mol. It is highly branched and has an average degree of polymerization of 2 million, making it one of the largest molecules in nature. Chain lengths of 20–25 glucose units between branch points are typical. About 70% of the mass of starch granule is regarded as amorphous and about 30% as crystalline. The amorphous regions contain the main amount of amylose but also a considerable part of the amylopectin. The crystalline region consists primarily of the amylopectin.



Basic structural design of (a) glucose units, (b) amylose, and (c) amylopectin

Sources of starch

Starch comprises mostly polysaccharide granules usually separated from the fully grown grains of corn (*Zea mays* Linn.); rice (*Oryza sativa* Linn.); and wheat (*Triticum aestivum* Linn.) and from the tubers of potato (*Solanum tuberosum* Linn.).

Applications of starch and modified starch in pharmacy

During recent years, starch has been taken as a new potential biomaterial for pharmaceutical applications because of the unique physicochemical and functional characteristics. Starch is composed of very small spherical or elliptical granules; it is colorless, odorless with slight characteristic taste, and insoluble in water and alcohol. In pharmaceutical industry, starch is important excipients that have been commonly employed because of its versatility and cheapness.

Starch as pharmaceutical excipients

Native starches were well explored as binder and disintegrate in solid dosage form, but due to poor flowability, their utilization is restricted. Most common form of modified starch, that is, pre-gelatinized starch marketed under the name of starch 1500, is nowadays most preferred directly compressible excipients in pharmaceutical industry. Recently, modified rice starch, starch acetate, and acid hydrolyzed discord a starch was established as multifunctional excipients in the pharmaceutical industry. The International Joint Conference on Excipients rated starch among the top ten pharmaceutical ingredients.

Starch as tablet disintegrant

They are generally employed for immediate release tablet formulations, where drug should be available within short span of time to the absorptive area. Sodium carboxymethyl starch (CMS), which is well established and marketed as sodium starch glycolate, is generally used for immediate release formulation. Some newer sources of starch have been modified and evaluated for the same.

Starch as controlled/sustained release polymer for drugs and hormones

Modified starches in different forms such as grafted, acetylated, and phosphate ester derivative have been extensively evaluated for sustaining the release of drug for better patient compliances. Starch-based biodegradable polymers, in the form of microsphere or hydrogel, are suitable for drug delivery. For example, high amylose corn starch has been reported to have good sustained release

properties and this has been attributed to its excellent gel-forming capacity. The mechanism of drug release from such gel forming matrices to be a result of the controlled passage of drug molecules through the obstructive gel layer, gel structure, and matrix.

Starch as plasma volume expander

Acetylated and hydroxyethyl starch are now mainly used as plasma volume expanders. They are mainly used for the treatment of patients suffering from trauma, heavy blood loss, and cancer.

Starch in bone tissue engineering

Starch-based biodegradable bone cements can provide immediate structural support and degrade from the site of application. Moreover, they can be combined with bioactive particles, which allow new bone growth to be induced in both the interface of cement-bone and the volume left by polymer degradation. In addition, starch-based biodegradable polymer can also be used as bone tissue engineering scaffold.

Starch in artificial red cells

Starch has also been used to produce a novel and satisfactory artificial RBCs with good oxygen-carrying capacity. It was prepared by encapsulating hemoglobin with long-chain fatty-acids-grafted potato starch in a self-assembly way.

Starch in nanotechnology

Starch nanoparticles, nanospheres, and nanogels have also been applied in the construction of nanoscale sensors, tissues, mechanical devices, and drug delivery system.

Starch microparticles

The use of biodegradable microparticles as a dosage form for the administration of active substances is attracting increasing interest, especially as a means of delivering proteins. Starch is one of the polymers that are suitable for the production of microparticles. It is biodegradable and has a long tradition as an excipient in drug formulations. Starch microparticles have been used for the nasal delivery of drugs and for the delivery of vaccines administered orally and intramuscularly. Bioadhesive systems based on polysaccharide microparticles have been reported to significantly enhance the systemic absorption of conventional drugs and polypeptides across the nasal mucosa, even when devoid of absorption enhancing agents. A major area of application of microparticles is as dry powder inhalations formulations for asthma and for deep-lung delivery of various agents. It has also been reported that particles reaching the lungs are phagocytosed rapidly by alveolar Macrophages. Although phagocytosis and sequestration of inhaled powders may be a problem for drug delivery to other cells comprising lung tissue, it is an advantage for chemotherapy of tuberculosis. Phagocytosed microparticles potentially can deliver larger amounts of drug to the cytosol than oral doses. It is also opined strongly that microparticles have the potential for lowering dose frequency and magnitude, which is especially advantageous for maintaining drug concentrations and improving patient compliance. This is the main reason this dosage form is an attractive pulmonary drug delivery system.

Starch microcapsules

Microencapsulation is the process of enclosing a substance inside a membrane to form a microcapsule. It provides a simple and cost-effective way to enclose bioactive materials within a semi-permeable polymeric membrane. Both synthetic/semi-synthetic polymers and natural polymers have been extensively utilized and investigated as the preparation materials of microcapsules. Although the synthetic polymers display chemical stability, their unsatisfactory biocompatibility still limits their potential clinical applications. Since the natural polymers always show low/non-toxicity, low immunogenicity, and thereafter good biocompatibility, they have been the preferred polymers used in microencapsulation

systems. Among the natural polymers, alginate is one of the most common materials used to form microcapsules; however, starch derivatives are now gaining attention. For instance, starch nasal bioadhesive microspheres with significantly extended half-life have been reported for several therapeutic agents, including insulin. Improved bioavailability of gentamycin-encapsulated starch microspheres as well as magnetic starch microspheres for parenteral administration of magnetic iron oxides to enhance contrast in magnetic resonance imaging has been reported.

Starch nanoparticles

Nanoparticles are solid or colloidal particles consisting of macromolecular substances that vary in size from 10 to 1000 nm. The drug may be dissolved, entrapped, adsorbed, attached, or encapsulated into the nanoparticles matrix. The matrix may be biodegradable materials such as polymers or proteins or biodegradable/biocompatible/ bioabsorbable materials such as starch. Depending on the method of preparation, nanoparticles can be obtained with different physicochemical, technical, or mechanical properties as well as modulated release characteristics for the immobilized bioactive or therapeutic agents.

Starch modification

Starch is rarely consumed in its intact form and frequently used by industry in its native form. Most native starches are limited in their direct application because they are unstable with respect to changes in temperature, pH, and shear forces. Native starches show a strong tendency for decomposition and retrogradation. In addition, some starch granules are inert, insoluble in water at room temperature, highly resistant to enzymatic hydrolysis, and consequently lacking in functional properties. Native starches are often modified to develop specific properties such as solubility, texture, adhesion, and tolerance to the heating temperatures used in industrial processes. Several methods have been developed to produce modified starches with a variety of characteristics and applications. All of these techniques alter the starch polymer, making it highly flexible and changing its physicochemical properties and structural attributes to increase its value for food and non-food industries. The starch modification industry is constantly evolving. Modifications of starch include physical, chemical, and enzymatic methods.

Chemical modification of starch

There are a number of chemical modifications made to starch to produce many different functional characteristics. The chemical reactivity of starch is controlled by their activity of its glucose residues. Modification is generally achieved through etherification, esterification, cross-linking, oxidation, and cationization, and grafting of starch. However, because of the dearth of new methods in chemical modifications, there has been a trend to combine different kinds of chemical treatments to create new kinds of modifications. The chemical and functional properties achieved following chemical modification of starch depends largely on the botanical or biological source of the starch, reaction conditions (reactant concentration, reaction time, pH, and the presence of catalyst), type of substituent, extent of substitution (degree of substitution [DS], or molar substitution), and the distribution of the substituent in the starch molecule. Chemical modification involves the introduction of functional groups into the starch molecule, resulting in markedly altered physicochemical properties. Such modification of native granular starches profoundly alters their gelatinization, pasting, and retrogradation behavior. The rate and efficiency of the chemical modification process depend on the reagent type, botanical origin of the starch, and on the size and structure of its granules. This also includes the surface structure of the starch granules, which encompasses the outer and inner surface, depending on the pores and channels.

Carboxymethylated starch

Starches can have hydrogen replaced by something else, such as a carboxymethyl group, making CMS. Adding bulky functional groups such as

carboxymethyl and carboxyethyl groups reduces the tendency of the starch to recrystallize and makes the starch less prone to damage by heat and bacteria. CMS is synthesized by reacting starch with monochloroacetic acid or its sodium salt after activation of the polymer with aqueous NaOH in slurry of an aqueous organic solvent, mostly alcohol. The total DS, that is, the average number of functional groups introduced in the polymer mainly determines the properties of the carboxymethylated products. It has an influence on disintegrating time of tablets and capsules.

Acetylated starch

Acetylated starch has also been known for more than a century. Starches can be esterified by modifications with an acid. When starch reacts with an acid, it loses a hydroxyl group, and the acid loses hydrogen. An ester is the result of this reaction. Acetylation of cassava starch has been reported to impart two very important pharmaceutical characters to it; increased swelling power and enhanced water solubility of the starch granules. Starch acetates and other esters can be made very efficiently on a micro-scale without addition of catalyst or water simply by heating dry starch with acetic acid and a hybrid eat 180°C for 2–10 min. At this temperature, starch will melt in acetic acid and thus, homogeneous acetylation would be expected to occur. Using acetic acid, starch acetates are formed, which are used as film-forming polymers for pharmaceutical products. A much recent scandium triflate catalyzed acetylation of starch at low to moderate temperatures. In general, starch acetates have a lower tendency to create gels than unmodified starch. Acetylated starches are distinguishable through high levels of shear strength. They are particularly stable against heat and acids and are equally reported to form flexible, water-soluble films.

Hydroxypropylated starch

Hydroxypropyl groups introduced into starch chains are said to be capable of disrupting inter- and intra-molecular hydrogen bonds, thereby weakening the granular structure of starch, leading to an increase in motional freedom of starch chains in amorphous regions. Such chemical modification involving the introduction of hydrophilic groups into starch molecules improves the solubility of starch and the functional properties of starch pastes, such as its shelf life, freeze/thaw stability, cold storage stability, cold water swelling, and yields reduced gelatinization temperature, as well as retarded retrogradation. Owing to these properties, hydroxypropylated starches are gaining interest in medicine. Hydroxypropylated starches of vary in amylose contents as sustained-release matrices in tablets monolithic matrix tablet formulation propranolol hydrochloride hydroxypropylation improved the sustained release ability of amylose containing starch matrices and conferred additional resistance to the hydrolytic action of pancreatin under simulated gastrointestinal conditions.

Succinylated starch

Modification of starch by succinylation has also been found to modify its physicochemical properties, thereby widening its applications in food and non-food industries such as pharmaceuticals, paper, and textile industries. Modification of native starch to its succinate derivatives reduces its gelatinization temperature and the retrogradation improves the freeze-thaw stability as well as the stability in acidic and salt-containing medium. In general, succinylated starch can be prepared by treating starches with different alkenyl succinic anhydride, for example, dodecenylsuccinic anhydride, octadecenyl succinic anhydride, or octenyl succinic anhydride. The incorporation of bulky octadecenyl succinic anhydride grouping to hydrophilic starch molecules has been found to confer surface-active properties to the modified starch. Unlike typical surfactants, octadecenyl succinic anhydride starch forms strong films at the oil-water interface giving emulsions that are resistant to reagglomeration. A recent application of succinylated starch in pharmaceuticals is preparation and characterization of acetyl succinate starch as a delivery carrier for bioactive food components pyridine-catalyzed esterification bovine serum albumin/ASA acetyl

succinate starch was found to be a potential carrier for colon-targeted drug delivery.

Phosphorylated starch

Phosphorylation was the earliest method of starch modification. The reaction gives rise to either monostarch phosphate or distarch phosphate (cross-linked derivative), depending upon the reactants and subsequent reaction conditions. Phosphate cross-linked starches show resistance to high temperature, low pH, and high shear and lead to increased stability of the swollen starch granule. The presence of a phosphate group in starch increases the hydration capacity of starch pastes after gelatinization and results in the correlation of the starch phosphate content to starch paste peak viscosity, prevents crystallization, and gel-forming capacity. These new properties conferred on starch by phosphorylation make them useful as disintegrants in solid dosage formulations and as matrix in agents. Interestingly, it has been documented that the only naturally occurring covalent modification of starch is phosphorylation. Conventionally, starch phosphorylation is carried out by the reaction of starch dispersion in water with reagents such as mono- or disodium orthophosphates, sodium hexametaphosphate, sodium tripolyphosphate, sodium trimetaphosphate, or phosphorus oxychloride. Alternative synthetic methods such as extrusion cooking, microwave irradiation, and vacuum heating have been reported. Phosphorylation using monosodium phosphate dehydrates ziprasidone. At low concentration, starch phosphate proved to be a better disintegrant than native starch in tablet formulation. Starch phosphates prepared by reactive extrusion as a sustained release agent. Reactive extrusion metoprolol tartrate starch phosphate prepared by reactive extrusion produced stronger hydrogels with sustained release properties as compared with native starch.

Co-polymerized starch

Chemical modification of natural polymers by grafting has received considerable attention in recent years because of the wide variety of monomers available. Graft copolymerization is considered to be one of the routes used to gain combinatorial and new properties of natural and synthetic polymers. In graft copolymerization, the guest monomer benefits the host polymer with some novel and desired properties in which the resultant copolymer gains characteristic properties and applications. As a rule, graft copolymerization produces derivatives of significantly increased molecular weight. Starch grafting usually entails etherification, acetylation, or esterification of the starch with vinyl monomers to introduce a reaction site for further formation of a polymeric chain. Such a chain would typically consist of either identical or different vinyl monomers (block polymers), or it may be grafted onto another polymer altogether. Graft copolymers find application in the design of various stimuli-responsive controlled-release (CR) systems such as transdermal films, buccal tablets, matrix tablets, microspheres/hydrogel bead system, and nanoparticulate system.

Calcium starch

Calcium starch, a new starch based polymer and to evaluate its application in CR. Calcium starch polymer was synthesized by gelatinization of starch in the presence of sodium hydroxide and cross-linking by treatment with calcium chloride. Potato starch (5 parts) was dispersed in purified water (50 parts) to form starch slurry. Sodium hydroxide (3 parts) was dissolved in water (30 parts) and the solution was added to starch slurry while mixing. Mixing was continued for 30 min to form a thick gelatinized mass. The mass formed was added to 300 mL of calcium chloride (20%w/v) solution contained in a vessel while stirring at 1000 rpm with a medium-duty stirrer. The stirring was continued for 1 h to precipitate calcium starch formed. The calcium starch formed was collected by vacuum filtration, washed repeatedly with water, and dried at 80°C. The dried polymer was powdered and passed through mesh No. 100.

Starch phosphate

Starch phosphate is one of the modified starches used in the frozen food industry. It is produced

by phosphorification of free hydroxyl groups of hydroglucose units of starch molecule. They are esterified with phosphate reagents. Phosphate reagents for starch phosphate monoester are orthophosphate salts. Starch phosphate production is normally using wet process 2. No reports are available units use as pharmaceutical excipient. Potato starch (100 g) and disodium hydrogen orthophosphate anhydrous (30 g) were suspended in 100 mL of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch mixture was conditioned for 12 h at room temperature (28°C). To enhance phosphorylation, this mixture was heated in a forced-air oven at 1300°C for 3 h. The product obtained was grounded and sized. Starch phosphate was insoluble in water and aqueous fluids of acidic and alkaline pHs. It also exhibited good swelling (400%) in water. It has no pasting or gelling property when heated at 100°C in water for 30 min. As starch phosphate exhibited good swelling in water, it is considered as a promising disintegrant in tablet formulations.

Starch citrate

Starch citrate prepared by reacting native starches such as potato, tacca, sago, and icacina with citric acid at elevated temperatures was crystalline, non-hygroscopic and was insoluble in water and aqueous fluids of acidic and alkaline pHs. It also exhibited good swelling (1500%) in water. It has no pasting or gelling property when heated at 100°C in water for 30 min. As starch citrate exhibited good swelling in water, it is considered as a promising disintegrant in tablet formulations and was evaluated as a disintegrant in tablet formulations. Citric acid (40 g) was dissolved in 100 ml of water and pH of the solution was then adjusted to 3.5 with 10 M sodium hydroxide. Citric acid (20 g) was dissolved in 20 ml of water, the pH of the solution was adjusted to 3.5 with 10 M sodium hydroxide and finally the volume was made up to 50 ml by adding water. The citric acid solution (50 ml) was mixed with 50 g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (28°C). The tray was then placed in a forced-air oven and dried at 60°C for 6 h. The mixture obtained was ground and further dried in a forced-air oven at 130°C for 2 h. The dry mixture was repeatedly washed with water to remove unreacted citric acid. The washed starch citrate was further dried at 50º C to remove the water/moisture completely.

Physical modification of starch

Physical modification of starch is mainly applied to change the granular structure and convert native starch into cold-water-soluble starch or small-crystallite starch. The major methods used in the preparation of cold-water-soluble starches involve instantaneous cooking-drying of starch suspensions on heated rolls (drum-drying) and spray-drying. A method for preparing granular cold-water-soluble starches by injection and nozzle-spray drying was developed. Among the physical processes applied to starch modification, high-pressure treatment of starch is considered an example of 'minimal processing. A process of iterated syneresis applied to the modification of potato, tapioca, corn, and wheat starches resulted in a new type of physically modified starches.

Drum drying method

When slurry of native starch is brought onto the hot surface of a drum, it will start to gelatinize (swell) almost immediately. The starch granules absorb water and their volume expands dramatically. The individual starch molecules are still held together in a greatly swollen reticulated network. However, the water will also start to evaporate at the same time, resulting in an open structure of the starch granules. When drum-dried starch is being dissolved in cold water, the granules will start to swell without the solution being heated; the so-called colds welling properties. The gelatinizing starch slurry on the drying drum becomes very viscous and sticky. It strongly adheres to the drum surface when passing then arrow gaps between the applicator rolls and the drying drum, by which a thin film is formed from which the remaining moisture can easily be evaporated before being scraped from the drum. Then arrow gaps are required for the best possible product quality but also

cause high shear forces. The shear forces vary when changing the gap distances. After a single rotation of the drying drum, the product film is scraped off by a knife, which is fixed in a heavy-duty knife holder. The knife holder needs to be a very rigid construction to ensure that the strong adhering product film will be removed over the entire length of the drum.

Spray drying of starch

Spray drying is a process which involves the rapid dehydration of moist particles which contain solids in either the soluble or insoluble form or both. Successful drying of these particles is largely dependent on the extent of atomization which has been preimposed on the feedstock to create these particles. A high viscosity is a deterrent to successful atomization in a spray-drying process. The viscosity of gelatinized starches in general terms increases progressively with a concentration of starch solids. This imposes a limitation in spray-drying systems since viscosities in excess of certain defined levels prevent successful atomization in the process of spray drying. Spray-dried gelatinized starches are of low bulk density. This can be directly attributed to the low solids concentrations required of present conventional spray-drying techniques, the process of the present invention consists of slurring starch, either gelatinized or ungelatinized starch, in water to provide slurry having solids content between about 10% and about 40%. The slurry is then pumped through a heater which heats the starch aqueous slurry to a temperature of at least about 325 F., preferably between about 325 and about 450 F. The slurry is maintained under pressure during heating and continued under pressure through the atomization step. The pressure is interdependent with viscosity, temperature, and apparatus. The pressure requirement is that necessary for atomization. Such pressure is in excess of that necessary to prevent vaporization of water in slurry of high solids at elevated temperatures. The heating time is that which is sufficient to allow substantially complete gelatinization and solubilization of the starch if previously ungelatinized. After heating, atomization is effected in a spray drier to a moisture content <15% and preferably <12%.

Pregelatinization of starch

It is the simplest starch modification, prepared by heating the slurry, roll drying, spray drying, or extrusion process. It maintains starch integrity while improving cold water thickening. This process is designed to enhance adhesiveness of starches. Pregelatinized starches exhibit good flow, binding, and compressibility and therefore enhanced their pharmaceutical acceptability.

Annealing

This is carried out by soaking the native starch in excess water between 40 and 60% w/w between gelatinization temperatures for a specific period of time. Annealed starch has decreased swelling characteristics [21], and the result an enhanced crystalline structure does not rupture the starch granules.

Enzymatic modification of starch

An alternative to obtaining modified starch is using various enzymes. This includes enzymes occurring in plants, for example, pullulanase and is amylase groups. Pullulanase is a 1,6- glycosidase, which statistically impacts the linear glucan, a pullulan which releases maltotriose oligomers. This enzyme also hydrolyses 1,6-glycoside bonds in amylopectin and dextrins when their side-chains include at least two 1,4- glycoside bonds. Isoamylase is an enzyme which totally hydrolyses 1,6-glycoside bonds in amylopectin, glycogen, and some branched maltodextrins and oligosaccharides but is characterized by low activity in relation to pullulan. In a study, starch granules were modified *in situ* using a reaction system in which glucoamylase reacts inside starch granules to give conversions of 10–50% D-glucose inside the granules.

Calcium starch

Chowdary *et al*. formulated and evaluated floating tablets of pioglitazone employing calcium starch, a new modified starch in comparison to hydroxypropyl methylcellulose K15M, a synthetic

cellulose derivative. Sodium bicarbonate as gas generating agent and beeswax as floating enhancer and the tablets were evaluated for *in vitro* buoyancy and drug release characteristics. Tablets formulated employing calcium starch (50%), sodium bicarbonate (10%), and beeswax (10%) exhibited floating over 36 h with a floating lag time of 5–10 min. Pioglitazone release from the floating tablets formulated was slow, spread over more than 24 h, and depended on the polymer used and its strength and concentration of sodium bicarbonate in the tablets. Drug release was diffusion controlled and followed first-order kinetics. Fickian diffusion was the drug release mechanism from all the tablets formulated. Calcium starch gave slow, controlled, and completes drug release in 24 h, whereas hydroxypropyl methylcellulose, K15M gives low but incomplete drug release. Calcium starch was found to be a better matrix former than hydroxypropyl methylcellulose for floating tablets.
Chowdary *et al*. synthesized calcium starch, a new starch-based polymer, and evaluated its application in CR and in the design of diclofenac CR tablets. Calcium starch polymer was synthesized by gelatinization of starch in the presence of sodium hydroxide and cross-linking by treatment with calcium chloride. Matrix tablets each containing 100 mg of diclofenac sodium were formulated employing calcium starch polymer in different proportions of drug and polymer and the tablets were evaluated. Diclofenac release from the formulated tablets was slow and spread over 24 h and depended on the percent polymer in the tablet. Release was diffusion-controlled and followed zero-order kinetics. Non-Fickian diffusion was the drug release mechanism from the formulated tablets. Diclofenac release from matrix tablets F3 formulated employing 15% calcium starch was similar to that from reacting SR tablets, a commercial sustained release formulation of diclofenac. Calcium starch polymer was found suitable for the design of oral CR tablets of diclofenac.
Chowdary *et al*. synthesized calcium starch, a new starch-based polymer, and evaluated its application in CR and in the design of diltiazem CR tablets. Calcium starch polymer was synthesized by gelatinization of starch in the presence of sodium hydroxide and cross-linking by treatment with calcium chloride. Matrix tablets each containing 90 mg of diltiazem hydrochloride were formulated employing calcium starch polymer in different proportions of drug and polymer and the tablets were evaluated. Diltiazem release from the formulated tablets was slow and spread over 24 h and depended on the percent polymer in the tablet. Fickian diffusion was the drug release mechanism from the formulated tablets. Diltiazem release from matrix tablets F3 formulated employing 15% calcium starch and F4 formulated employing 20% calcium starch were similar to that from Dilzem SR and DTM 90 SR tablets, respectively. Calcium starch polymer was found suitable for the design of oral CR tablets of diltiazem.
Chowdary *et al*. synthesized calcium starch, a new starch-based polymer, and evaluated its application in CR and in the design of gliclazide CR tablets. Calcium starch polymer was synthesized by gelatinization of starch in the presence of sodium hydroxide and cross-linking by treatment with calcium chloride. Matrix tablets each containing 30 mg of gliclazide were formulated employing calcium starch polymer in different proportions of drug and polymer and the tablets were evaluated. Gliclazide release from the formulated tablets was slow and spread over 24 h and depends on the percent polymer in the tablet. Non-Fickian diffusion was the drug release mechanism from the formulated tablets. Gliclazide release from matrix tablets F3 formulated employing 5% calcium starch was similar to that from Diamicron MR Tablets, a commercial sustained release formulation of gliclazide. Calcium starch polymer was found suitable for the design of oral CR tablets of gliclazide.

Preparation of calcium starch

Potato starch (5 parts) was dispersed in purified water (50 parts) to form starch slurry. Sodium hydroxide (3 parts) was dissolved in water (30 parts) and the solution was added to starch slurry while mixing. Mixing was continued for 30 min to form a thick gelatinized mass. The mass formed was added to 300 mL of calcium chloride (20 %

w/v) solution contained in a vessel while stirring at 1000 rpm with a medium-duty stirrer. The stirring was continued for 1 h to precipitate calcium starch formed. The calcium starch formed was collected by vacuum filtration, washed repeatedly with water, and dried at 80ºC. The dried polymer was powdered and passed through mesh No. 100.

MATERIALS AND METHODS

Experimental methodology

Materials used

S. No.	Name of the material	Manufacturing/ supplying company
1	Metoprolol tartrate	Apogen Pharma Pvt. Limited
2	Sodium hydroxide	Fisher scientific
3	Calcium chloride	Fisher scientific
4	Starch	SD Fine Chemicals Limited
5	Potato starch	SD Fine Chemicals Limited
6	Cornstarch	SD Fine Chemicals Limited
7	Rice starch	SD Fine Chemicals Limited
8	Magnesium stearate	SD Fine Chemicals Limited
9	Talc	SD Fine Chemicals Limited
10	Isopropyl alcohol	Fisher scientific

Instrumentation used

S. No.	Name of the instrument	Manufacturer/supplier and model number
1	Electronic balance	Shimadzu, AY–200,Japan
2	Digital P^H meter	Elico Ltd, Hyderabad, μP^H systems361
3	16 Station rotary tablet compression machine	Cadmach, Ahmedabad
4	Hardness tester	Monsanto, Mumbai
5	Roche friabilator	Cadmach, Ahmedabad
6	Tapped density apparatus	Campbell Electronics, Mumbai
7	Dissolution test apparatus	Electrolab,TDT08L,dissolution tester, USP
8	UV–Visible spectrophotometer	ELICOSL159,ShimadzuUV spec1700
9	Hot air oven	Thermolab, GMP model
10	Perkin Fourier Transform Infrared Spectrophotometer	Shelton, USA

Construction of standard calibration curve of Metoprolol tartrate

Accurately weighed amount of metoprolol tartrate (100 mg) was transferred into a 100 ml volumetric flask and dissolved in 10 ml of buffer (6.8 phosphate buffer). Then, the volume was made up to the mark with the help of buffer to give a stock solution of1mg/ml. From the above stock solution, a series of dilutions ranging from 5 to 30 µg/ml were prepared using buffer (6.8 phosphate buffer). Then, the absorbance was measured using a double beam UV-spectrophotometer at 223 nm.

Concentration(µg/ml)	Absorbance (X±SD)
5	0.125±0.0052
10	0.278±0.0035
15	0.421±0.0031
20	0.571±0.0028
25	0.796±0.007
30	0.989±0.0091

Preformulation studies

Drug-excipient compatibility is an important part to understand the role of inactive ingredients in product quality [Tables 1-3]. It is based on the physicochemical characteristics of the drug substance and its impurity excipients used in the formulation. The results of preformulation studies are used to set the processing conditions and selection of packing containers. Metoprolol tartrate-selected excipients and mixtures were subjected to IR spectral study to detect the interactions between the drug and selected inactive ingredients. The drug excipients mixtures were prepared by blending the drug and excipients in 1:1 ratio. The resulting blend was transferred into a vial and sealed properly. Such sealed vials were kept in a stability chamber and maintained at 40 ± 0.2°C, 75 ± 0.5% RH. The vials were stored for a period of 1 month. The samples were withdrawn and subjected to IR studies by KBR pellet technique. The physicochemical compatibility between metoprolol tartrate and excipients used in this work was carried out by subjecting to IR spectral studies using Perkin Fourier Transform Infrared (FT-IR) spectrophotometer (Shelton USA). The samples were scanned within the wavelength region between 3923cm^{-1} to 665 cm^{-1}. The spectra obtained for metoprolol tartrate and physical mixtures metoprolol tartrate blended.

KBr Pell ET procedure for solid samples

Take about 1/8" of the solid sample on a micro spatula and about 0.25–0.50 teaspoons of KBr. Mix thoroughly in a mortar while grinding with the pestle. If the sample is in large crystals, grind the sample separately before adding KBr. Place just enough spl. to cover bottom in pellet dies. Place in press and press at 5000–10000 psi. Check pellet press brochure for details. Carefully remove the pressed sample from die and place in the FTIR sample holder. The pressed disc should be nearly clear if properly made. If it is translucent, regrind, and repress.

Preparation of modified starch

Preparation of calcium starch

Potato starch (5 parts) was dispersed in purified water (50 parts) to form starch slurry. Sodium hydroxide (3 parts) was dissolved in water (30 parts) and the solution was added to starch slurry while mixing. Mixing was continued for 30 min to form a thick gelatinized mass. The mass formed was added to 300 mL of calcium chloride (20% w/v) solution contained in a vessel while stirring at 1000 rpm with a medium-duty stirrer. The stirring was continued for 1 h to precipitate calcium starch formed. The calcium starch formed was collected by vacuum filtration, washed repeatedly with water, and dried at 80°C. The dried polymer was powdered and passed through mesh No. 100.

Evaluation of modified starch

The prepared modified starch was evaluated using FT-IR studies, after conducting FT-IR studies, it is confirmed that the basic structure of starch is not disturbed or destroyed by the chemical modification.

The comparison between starch and calcium starch used in this work was carried out by subjecting to IR spectral studies using Perkin FT-IR spectrophotometer (Shelton USA). The samples were scanned within the wavelength region between 3923cm^{-1} and 665 cm^{-1}.

Conformation of starch modification

When the wavenumbers for stretching and bending of starch before and after modification were compared and the differences were observed between the wavenumbers for same functional groups. By this, we can say that the changes in structure of starch are done successfully.

In starch, we observed two peaks for alcoholic (-OH) groups but only one peak was observed in Calcium starch for the same group.it means one of the alcoholic hydroxyl groups is replaced by calcium and cross-linking was occur at that particular group.

The IR spectrum of starch was shown in Figure 1 and the following characteristic peaks were observed in spectra of calcium starch.

3721 cm^{-1} - O-H Stretching
2928 cm^{-1} - C – H Stretching
1148 cm^{-1} - C–O Stretching

The IR spectrum of calcium starch was shown in Figure 5 and the following characteristic peaks were observed in spectra of starch.

3430 cm^{-1} - O – H Stretching
2922.69 cm^{-1} - C–H Stretching
1079 cm^{-1} - C–O Stretching

Preparation of granules

The required quantities of medicament and matrix materials were mixed thoroughly in a mortar. The binder solution (mixture of alcohol and purified water at 1:1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 24 to obtain wet granules. The wet granules were dried at 60° for 4 h.

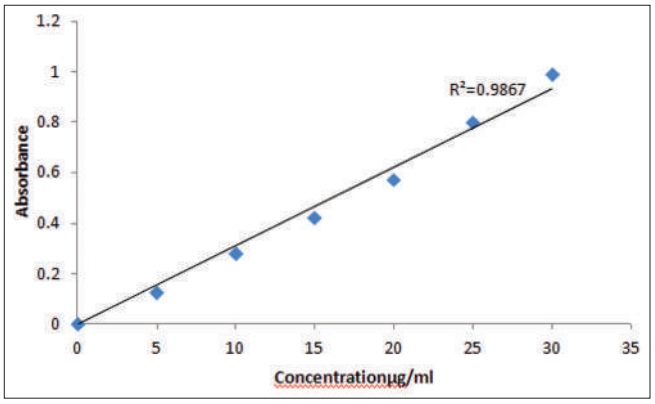


Figure 1: Standard calibration curve of metoprolol tartrate

Evaluation of granules

Studies on micromeritic properties of the blend [3, 4]

Bulk density

One gram of drug-polymer was weighed separately and transferred into a 10 ml measuring cylinder. Then, the bulk volume was noted. The bulk density was calculated using the following formulae.

Bulk density (g/ml) =Mass of the powder/Bulk volume.[1-7]

Tapped density

One gram of drug-polymer was weighed separately and transferred into a 10 ml measuring cylinder and subjected to 200 tapping. Then the volume was noted as tapped volume and calculated using the following formulae.

Tapped density (g/ml) =Mass of the powder/ Tapped volume

Carr's index

One gram of drug-polymer was weighed separately and transfer red into a 10 ml measuring cylinder and subjected to 200 tapping. Then the volume was noted as tapped volume. Carr's index was calculated using the following formulae.

Carr's index (%) =Tapped density–Bulk density/ Tapped density×100

% compressibility	Flow description
5–15	Excellent
12–16	Good
18–21	Fair
23–28	Poor
28–35	Very Poor
35–38	Very Very Poor
> 40	Extremely Poor

Hausner's ratio

It was determined by comparing the tapped density to the bulk density using the following formulae.

Hausner's ratio (%)=Tapped density/Bulk density.

Hausner's ratio	Type of flow
<1.25	Good flow
1.25–1.5	Moderate flow
More than 1.5	Poor flow

Preparation of tablets

Tablets each containing 105 mg of metoprolol tartrate equivalent to 100 mg of metoprolol succinate were prepared employing calcium starch in different proportions of drug and polymer. The required quantities of medicament and matrix materials were mixed thoroughly in a mortar. The binder solution (mixture of alcohol and purified water at 1: 1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 24 to obtain wet granules. The wet granules were dried at 60° for 4 h. The tablet granules were compressed into tablets on a rotary multi-station tablet punching machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad) to a hardness of 8–10 kg/sq.cm. Using 9 mm and 12 mm round and flat punches.

Evaluation of tablets

Thickness

The thicknesses of formulated tablets were measured using Vernier Calipers.

Weight variation test

Twenty tablets were collected and were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated using the following formulae.

%weight variation=Average weight–Individual weight/Average weight×100.

Hardness

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and zero reading was taken. The lower plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was calculated by deducting the initial pressure from the final pressure.

Friability

Friability of the tablets was determined using Roche friabilator. Thirty-two tablets were weighed and placed in the friabilator and were subjected to 25 revolutions per 4 min. Tablets were then dedusted, reweighed, and percentage loss was calculated. Friability is obtained by the following formulae.
%Friability =Initial weight –Final weight/Initial weight×100

Drug content determination

Five tablets were collected, powdered, and powder containing the equivalent to 100 mg of drug was dissolved in 100 ml of buffer (water). Then, the solution was filtered, suitably diluted, and analyzed for metoprolol tartrate by measuring the absorbance spectrophotometrically at 223 nm.

In vitro dissolution studies

In vitro dissolution studies for metoprolol tartrate extended-release tablets were performed in 6.8 phosphate buffer using USP type II dissolution test apparatus with paddle stirrer, the stirring speed employed was 50 rpm, and the temperature was maintained at 37 ± 0.5°C. Samples were withdrawn at different time intervals and replaced with fresh dissolution medium; solutions were filtered and determined for Metoprolol tartrate content by UV-Spectrophotometer at 223 nm.

Calculation of similarity factor

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f2 = 50^* \log \{[1+ (1/n) \sum(R-T)]^{-0.5} * 100\}.$$

The dissolution test performed for the tablets and the results were compared with the standard values for percentage drug release specific for metoprolol mentioned in USP.

Time (in hours)	Amount dissolved (%)
1	NMT25
4	20-40
8	40-60
20	NLT80

EXPERIMENTAL RESULTS

Formulation code	correlation coefficient(r)value					T50 (h)	f_2
	Zero order	First order	Higuchi	Peppas	Release rate constant k_0(mg/h)		
F1	0.9841	0.8354	0.9351	0.9816	2.03 (mg/min)	24.6 (min)	7.8
F2	0.9858	0.9212	0.9699	0.9956	12.2684	4.1	28.35
F3	0.985	0.9292	0.9659	0.9962	8.8517	5.6	44.05
F4	0.9798	0.8972	0.969	0.999	6.3119	7.9	56.73
F5	0.9948	0.8509	0.9232	0.9751	4.707	10.6	52.23

Comparative metoprolol release profiles observed from the tablets formulated with different types of calcium starch.

Time (hours)	% drug release		
	F4	F8	F11
0	0	0	0
1	12.24±2.25	11.08±3.09	9.19±3.02
2	19.46±2.65	18.87±2.17	14.36±2.34
3	27.48±2.36	22.25±2.33	21.17±1.81
4	33.84±2.50	25.36±2.28	26.45±2.25
5	39.39±1.88	29.09±3.78	31.2±2.36
6	42.38±3.54	34.01±1.57	33.83±3.09
7	49.75±2.44	36.95±2.50	38.07±1.95
8	54.72±1.46	42.38±1.77	42.78±2.38
9	62.21±3.12	46.7±2.20	48.56±1.70
10	67.00±1.56	51.2±2.78	51.77±2.72
11	68.95±1.69	53.72±3.01	55.17±1.98
12	72.93±2.30	56.98±2.95	59.16±3.64
13	79.27±2.47	64.03±2.77	66.1±1.77
14	84.35±1.60	68.55±2.47	70.05±2.56
15	87.31±2.61	71.07±1.95	72.59±2.82
16	96.96±2.54	76.65±1.32	78.19±1.65
17		79.82±1.61	83.55±3.46
18		86.93±1.86	86.63±2.42
19		91.64±2.97	91.19±1.70
20		98.85±2.91	98.85±2.53

RESULTS AND DISCUSSION

The Studies were undertaken to study the effect of various starches such as potato starch, corn starch, rice starch modified as calcium starch on physical characters and *in-vitro* drug release of metoprolol tartrate from the formulated sustained release tablets.

Compatibility studies

The drug and selected starches blends were subjected to drug excipient compatibility studies using FT-IR studies and the results are presented from Figure 7 and the following characteristic peaks were noticed. The IR spectrum of metoprolol tartrate was shown in Figure 4 and the following characteristic peaks were observed in spectra of metoprolol tartrate.

The following functional groups were identified.

Functional Group	Absorption (cm^{-1})	Intensity	Functional Group	Absorption (cm^{-1})	Intensity
Alkene =C-H	3020-3100	Medium	Alcohol O-H	3400-3650	Medium, broad
Alkene C=C	1640-1680	Medium	Alcohol C-O	1050-1150	Medium
Arene C-H	3030	Weak	Carboxylic acid O-H	2500-3100	Strong, broad
Arene C=C	1660-2000 1450-1600	Weak Medium	Carboxylic acid C=O	1710	Strong
Alkyne ≡C-H	3300	Strong	Ester C=O	1735	Strong
Alkyne C≡C	2100-2260	Medium	Ester sp^2 C-O	1200-1250	Strong
Nitrile C≡N	2210-2260	Medium	Ester sp^3 C-O	1000-1100	Strong
Alkyl halide C-Cl	600-800	Strong	Aldehyde C=O	1730	Strong
Alkyl halide C-Br	500-600	Strong	Aldehyde C-H	2720	Weak
Amine N-H	3300-3500	Medium	Ketone C=O	1715	Strong
Amine C-N	1030-1230	Medium	Amide C=O	1690	Strong

3460.52 cm^{-1} - OH Stretching
2873 cm^{-1} - C – H Stretching
1513.41 cm^{-1} - Ar –C=C Stretching
1358.91 cm^{-1} - C–N Stretching
1250 cm^{-1} - C – O Stretching
3460.52 cm^{-1} - N –H Bending

The IR spectrum of starch was shown in Figure 2 and the following characteristic peaks were observed in spectra of calcium starch.

3721 cm^{-1}- O – H Stretching
2928 cm^{-1}- C – H Stretching
1148 cm^{-1}- C–O Stretching

The IR spectrum of calcium starch was shown in Figure 3 and the following characteristic peaks were observed in spectra of starch.

3430 cm^{-1}- O – H Stretching
2922.69 cm^{-1}- C – H Stretching
1079 cm^{-1}- C– Stretching

The IR spectrum of metoprolol tartrate + calcium starch (potato) was shown in Figure 5 and the following characteristic peaks were observed in spectra of metoprolol tartrate + calcium starch (potato).

3393.52 cm^{-1} -O–H Stretching
873.59 cm^{-1} -C – H Stretching
1512.15 cm^{-1} -Ar –C=C Stretching
1244.05 cm^{-1} -C–N Stretching
1080 cm^{-1} -C–O Stretching
3393.87 cm^{-1} -N–H Bending

The IR spectrum of metoprolol tartrate + calcium starch (corn) was shown in Figure 6 and the following characteristic peaks were observed in spectra of metoprolol tartrate +calcium starch (corn).

3271.24 cm^{-1} -O–H Stretching
764.56 cm^{-1} -C – H Stretching
1512.48 cm^{-1} -Ar –C=C Stretching
1322.91 cm^{-1} -C–N Stretching
1244.05 cm^{-1} -C– O Stretching
3377.70 cm^{-1}-N –H Bending

The IR spectrum of metoprolol tartrate + calcium starch (rice) was shown in Figure 7 and the following characteristic peaks were observed in spectra of metoprolol tartrate + calcium starch (rice).

3381.48 cm^{-1}- O – H Stretching
703.57 cm^{-1} -C – H Stretching
1512.46 cm^{-1} -Ar –C=C Stretching
1322.91 cm^{-1} -C– N Stretching
1243.92 cm^{-1} -C – O Stretching
3381.48 cm^{-1} -N –H Bending

As the principle peaks observed were identical in the spectra of drug and spectra of various mixtures, so it was confirmed that no chemical or physical interaction exists between the drug and the excipients employed in this investigation.

Micromeritics, physical parameters, and *in vitro* release studies on metoprolol tartrate formulated with calcium starch prepared using potato starch

The blend containing metoprolol tartrate and selected calcium starch with different ratios were evaluated for micromeritic properties, and results were reported in Table 4. The observed Hausner's ratio was found in between 1.12 and 1.16 and Carr's index in between 11.29 and 13.46. These results are indicating that the blends are exhibiting good flow property and hence they were subjected to compression. All the formulated tablets (F1 to F5)

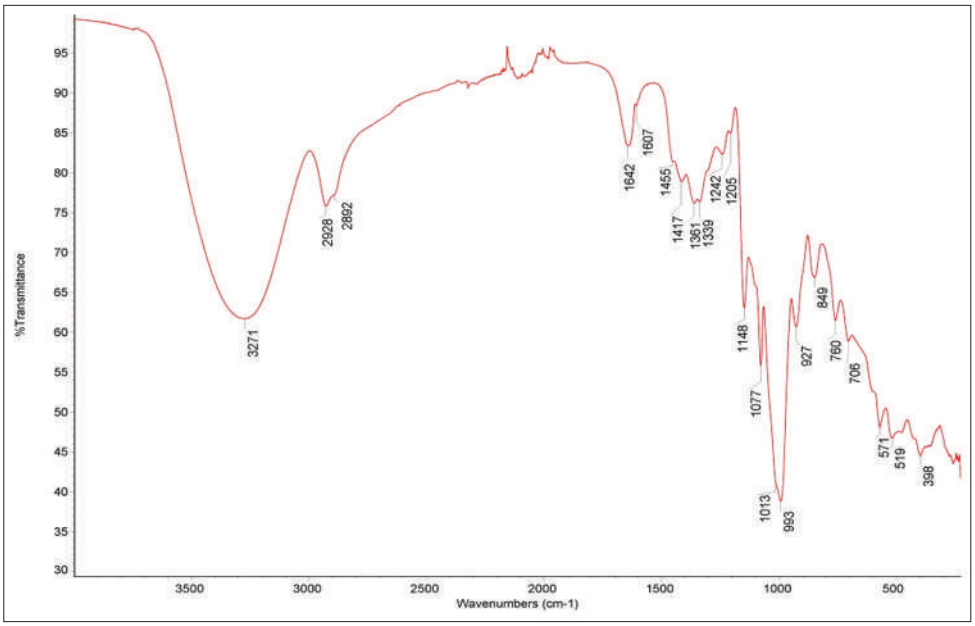


Figure 2: Fourier transform infrared spectra of Starch

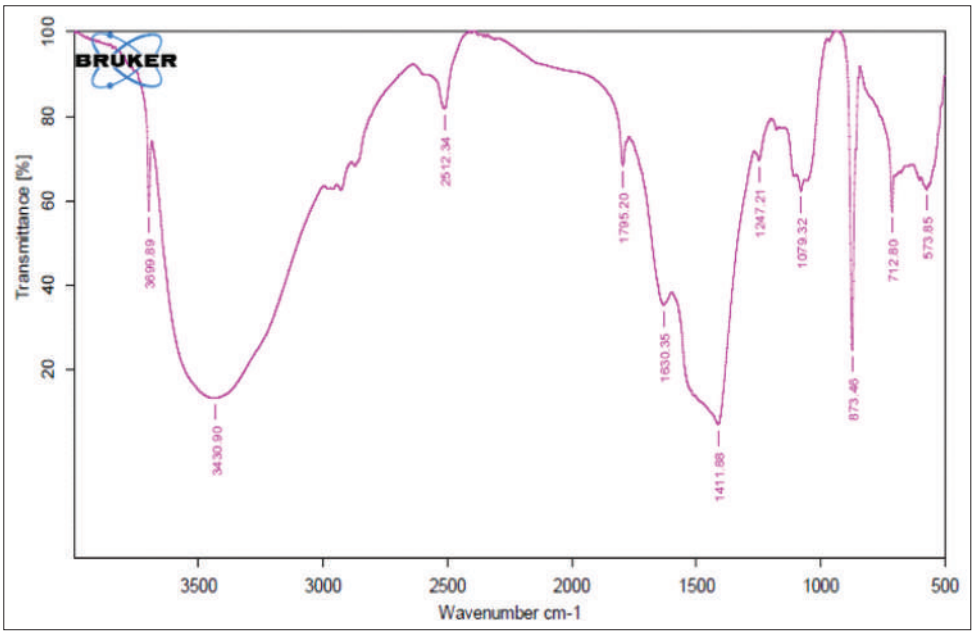


Figure 3: Fourier transform infrared spectra of calcium starch

were evaluated for thickness, hardness, friability, weight variation, drug content, and the results were reported in Table 5. From the observed results, all the formulated tablets found to satisfy the quality control requirements and are within limits as per IP. The tablets were subjected to *in-vitro* release studies and the data were reported in Tables 6 and 6.4 and the comparative. *In-vitro* release profiles graph were depicted in Figures 6 and 7. The percentage of drug release for formulations F1 to F5 was found to be 94.75 (50 min), 94.37 (9 h), 93.60 (12 h), 96.96 (16 h), and 97.41 (20 h), respectively. The release kinetics followed zero-order kinetics and the results were reported in Table 6.7 and the graph depicted between cumulative amount of drug release versus time [in Figures 9 and 10] was found to be linear. The mechanism of drug release was found to be diffusion and erosion (Peppas) type and the graph depicted between log time versus log cumulative % of drug release [Figures 11 and 12] was found to be linear and the drug release from the formulations F2-, F5 followed non-Fickian type of mechanism The

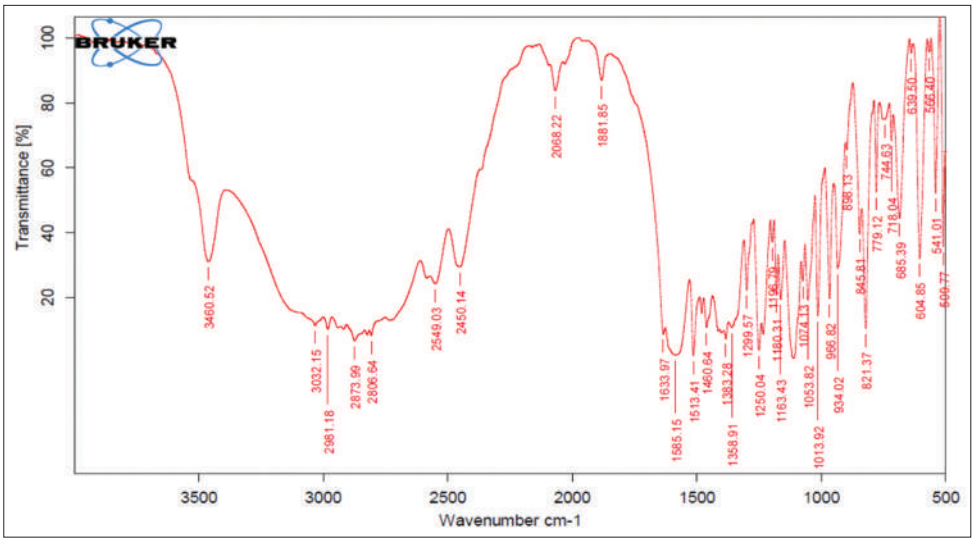


Figure 4: Fourier transform infrared spectra of metoprolol tartrate

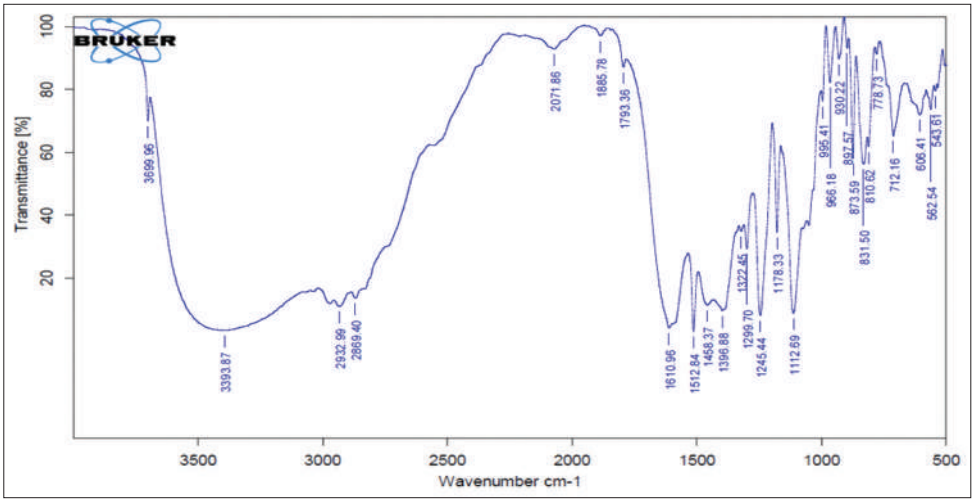


Figure 5: Fourier transform infrared spectra of metoprolol tartrate + calcium starch (Potato)

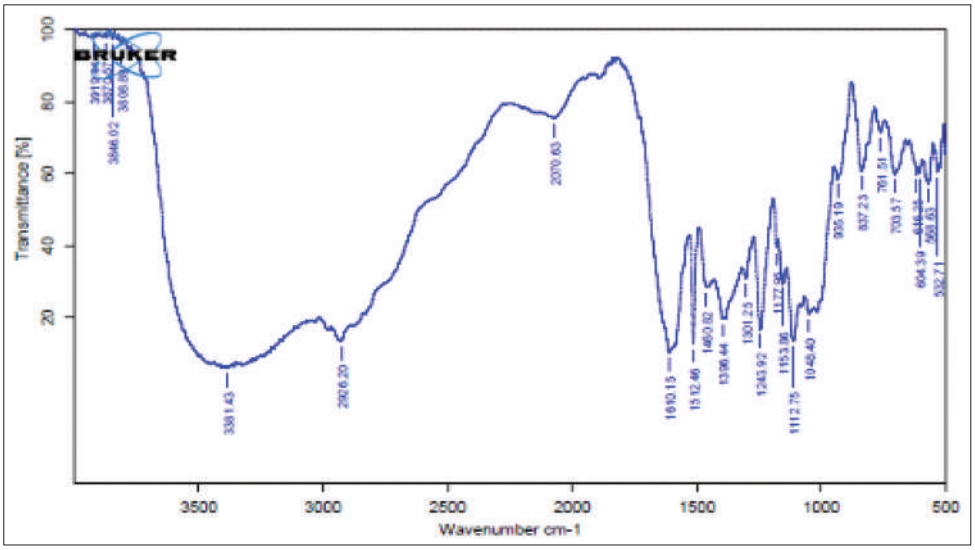


Figure 6: Fourier transform infrared spectra of metoprolol tartrate + calcium starch (Rice)

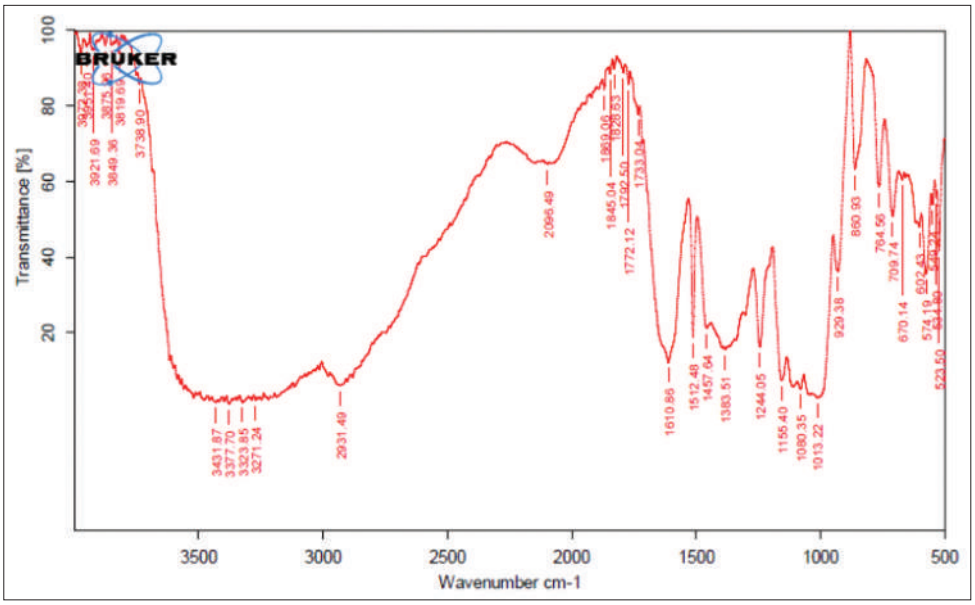


Figure 7: Fourier transform infrared spectra of metoprolol tartrate + calcium starch (Corn)

Table 1: Composition of metoprolol tartrate extended-release tablets formulated with starch and calcium starch prepared by potato starch

Ingredient's	Quantity(mg) per tablet				
	F1	F2	F3	F4	F5
Metoprolol tartrate	105	105	105	105	105
starch	100	-	-	-	-
Calcium starch(potato)	-	100	200	300	400
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5
Total	215	215	315	415	515

Table 2: Composition of metoprolol tartrate extended-release tablets formulated with calcium starch prepared using corn starch

Ingredient's	Quantity(mg) per tablet		
	F6	F7	F8
Metoprolol tartrate	100	100	100
Calcium starch(corn)	100	200	300
Magnesium stearate	5	5	5
Talc	5	5	5
Total	215	315	415

Table 3: Composition of metoprolol tartrate extended-release tablets formulated with calcium starch prepared using rice starch

Ingredient's	Quantity (mg) per tablet		
	F9	F10	F11
Metoprolol tartrate	105	105	105
Calcium starch(rice)	100	200	300
Magnesium stearate	5	5	5
Talc	5	5	5
Total	215	315	415

Table 4: Micromeritic properties of blend containing metoprolol tartrate and calcium starch prepared using potato starch

Formulation code	Bulk density (gm/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio (%)
F1	0.54±0.24	0.63±0.19	12.73±1.25	1.13±0.05
F2	0.55±0.36	0.62±0.31	11.29±1.06	1.12±0.03
F3	0.51±0.25	0.58±0.26	12.06±1.65	1.16±0.05
F4	0.58±0.14	0.67±0.15	13.43±1.41	1.15±0.02
F5	0.52±0.17	0.60±0.30	13.33±1.28	1.15±0.06

observed exponential coefficient values from Peppas plots were found to be 0.71, 0.71, 0.73, and 0.74 from these formulations. Various *in-vitro* dissolution parameters such as K, $t_{50,}$ t_{90}, and similarity factor (f_2) were calculated and the results were reported in Table 6.7. Statistical treatments of *in-vitro* parameters for modified starches were reported in Table 8 and they found to be statistically significant [Figure 8].

Micromeritics, physical parameters, and *in vitro* release studies on metoprolol tartrate formulated with calcium starch prepared using corn starch

The blend containing metoprolol tartrate and selected calcium starch with different ratios were evaluated for micromeritic properties, and results

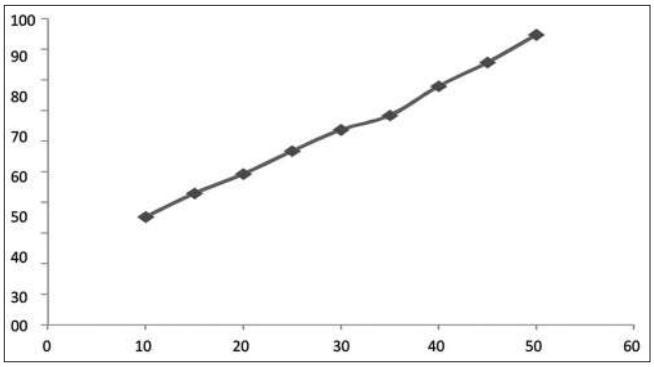


Figure 8: *In vitro* release profiles observed from metoprolol tartrate tablets formulated with starch

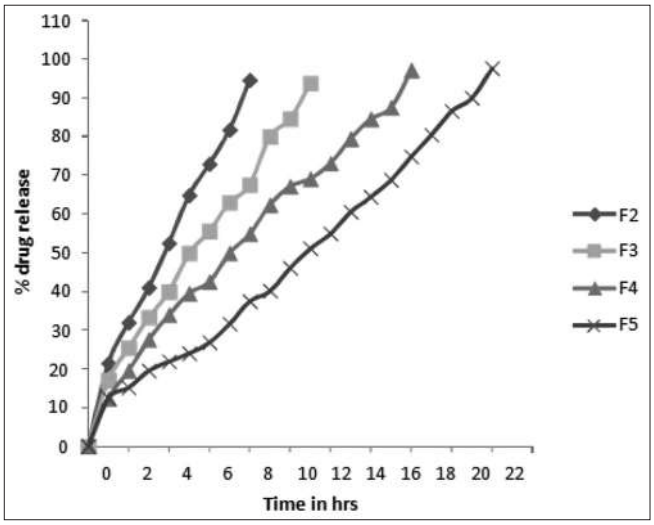


Figure 9: *In vitro* release profiles observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using potato starch

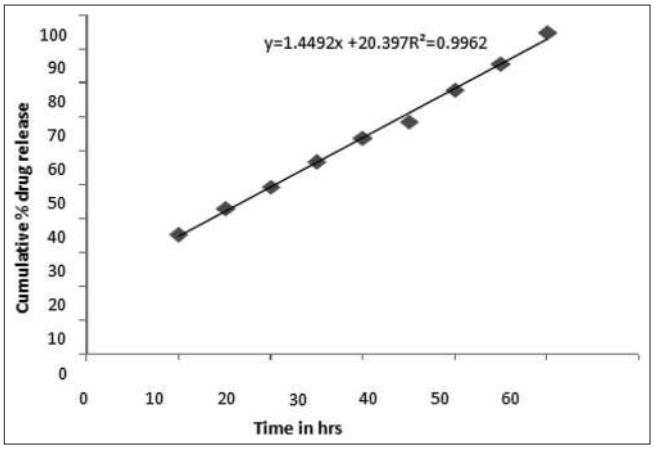


Figure 10: Zero-order plots observed from metoprolol tartrate tablets formulated with different ratios of Calcium Starch prepared using starch

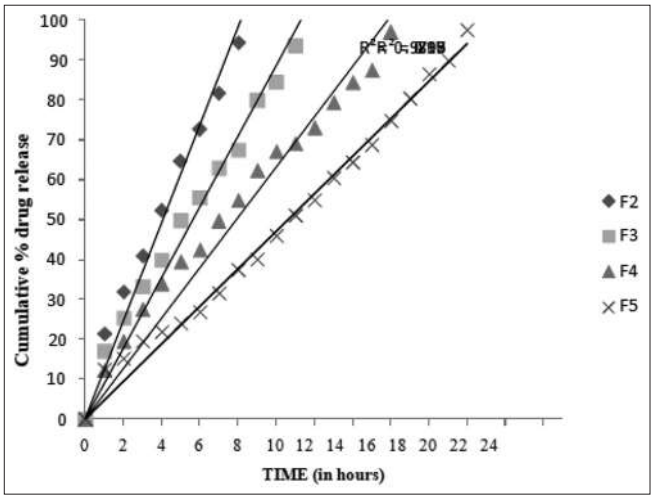


Figure 11: Zero-order plots observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using potato starch

were reported in Table 9. The observed Hausner's ratio was found in between 1.09 and 1.23 and Carr's index in between 5.71 and 11.26. These results are indicating that the blends are exhibiting good flow property and hence they were subjected to compression. All the formulated tablets (F6 to F8) were evaluated for thickness, hardness, friability, weight variation, drug content, and the results were reported in Table 10. From the observed results, all the formulated tablets found to satisfy the quality control requirements and are within limits as per IP.

The tablets were subjected to *in-vitro* release studies and the data were reported in Table 11 and the comparative *in-vitro* release profiles graph were depicted in Figure 13. The percentage of drug release for formulations F6 to F8 was found to be 90.33 (8 h), 95.44 (15 h), and 98.85 (20 h), respectively. The release kinetics follows zero-order as the results were reported in Table 12 and the graph depicted between cumulative amount of drug release versus time [in Figure 14] was found to be linear. The mechanism of drug release was found to be diffusion and erosion (Peppas) type and the graph depicted between log time versus log cumulative % of drug release [in Figure 15] was found to be linear and the drug release from the formulations F6, F7, F8 followed non-Fickian type of mechanism. The observed exponential coefficient values from Peppas plots were found to be 0.61, 0.68, and 0.72 from these formulations.

Various *in-vitro* dissolution parameters such as K,

Table 5: Physical characters of metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using potato starch

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Average weight (mg)	Friability (%)	Drug content (%)
F1	4.17±0.22	4.2±0.09	216.2±0.05	0.67±0.04	97.74±0.3
F2	4.11±0.36	4.5±0.04	216.6±0.03	0.69±0.05	98.1±0.5
F3	3.85±0.23	4.1±0.1	314.4±0.02	0.72±0.08	97.04±0.3
F4	4.08±0.17	4.3±0.06	417.2±0.04	0.63±0.04	98.3±0.6
F5	4.27±0.27	4.5±0.07	517.4±0.03	0.84±0.07	98.7± 0.3

Table 6: *In vitro* release observed from metoprolol tartrate tablets formulated with Starch

Time (min)	% drug release
5	25.3±2.17
10	35.3±1.98
15	42.97±2.48
20	49.31±3.03
25	56.8±2.28
30	63.73±1.85
35	68.4±2.87
40	77.93±3.21
45	85.68±2.41
50	94.75±2.19

$t_{50,}t_{90}$, and similarity factor (f_2) were calculated and the results were reported in Table 12. Statistical treatments of *in-vitro* parameters (one-way ANOVA) for modified starches were reported in Table 13 and they found to be statistically significant.

Micromeritics, physical parameters, and *in vitro* release studies on metoprolol tartrate formulated with calcium starch prepared using rice starch

The blend containing metoprolol tartrate and selected calcium starch with different ratios were evaluated for micromeritic properties, and results were reported in Table 14. The observed Hausner's ratio was found in between 1.13 and 1.16 and Carr's index in between 11.94 and 14.06. These results are indicating that the blends are exhibiting good flow property and hence they were subjected to compression. All the formulated tablets (F9 to F11) were evaluated for thickness, hardness, friability, weight variation, drug content, and the results were reported in the Table 15. From the observed results, all the formulated tablets found to satisfy the quality control requirements and are within limits as per IP.

Table 7: *In vitro* release observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using potato starch

Time (hours)	% drug release			
	F2	F3	F4	F5
0	0	0	0	0
1	21.37±1.90	17.02±2.43	12.24±2.25	12.38±1.85
2	31.87±2.70	25.31±2.75	19.46±2.65	15.11±3.75
3	40.88±1.81	33.24±3.06	27.48±2.36	19.47±3.35
4	52.30±1.93	39.80±2.47	33.84±2.50	21.83±1.64
5	64.70±2.53	49.76±1.67	39.39±1.88	23.93±2.37
6	72.73±2.64	55.46±1.56	42.38±3.54	26.77±2.25
7	81.55±2.37	62.81±2.31	49.75±2.44	31.52±2.75
8	94.37±3.11	67.33±2.78	54.72±1.46	37.33±1.93
9		79.86±1.93	62.21±3.12	40.01±2.21
10		84.39±2.87	67.00±1.56	45.90±2.86
11		93.60±3.13	68.95±1.69	50.98±1.37
12			72.93±2.30	54.79±3.24
13			79.27±2.47	60.38±2.43
14			84.35±1.60	64.28±1.96
15			87.31±2.61	68.65±3.21
16			96.96±2.54	74.65±2.96
17				80.27±2.52
18				86.38±3.28
19				89.78±1.52
20				97.41±3.08

The tablets were subjected to *in-vitro* release studies and the data were reported in Table 16 and the comparative *in-vitro* release profiles graph were depicted in Figure 16. The percentage of drug release for formulations F9 to F11 was found to

be 89.72 (10 h), 97.07 (15 h), and 98.85 (20 h), respectively. The release kinetics follows zero-order as the results were reported in Table 17 and the graph depicted between cumulative amount of drug release versus time [in Figure 17] was found to be linear. The mechanism of drug release was found to be diffusion and erosion (Peppas) type and the graph depicted between log time versus log cumulative % of drug release [in Figure 18] was found to be linear and the formulations F9, F10, F11 (0.71, 0.76, 0.79) followed non-Fickian type of mechanism. Various *in-vitro* dissolution parameters such as K, $t_{50,}$ t_{90}, and similarity factor (f_2) were calculated and the results were reported in Table 17. Statistical treatments of *in-vitro* parameters for modified starches were reported in Table 18 and they found to be statistically significant.

Table 8: ANOVA for formulations of metoprolol tartrate and calcium starch (potato)

	Parameter	A Value	B Data Set-B	C Data Set-C	D Data Set-D
		Y	Y	Y	Y
1	Table Analyzed				
2	Data 1				
3	One-way analysis of variance				
4	P value	P<0.0001			
5	P value summary	***			
6	Are means signif. different? (P < 0.05)	Yes			
7	Number of groups	3			
8	F	128100			
9	R squared	1.000			
10					
11	ANOVA Table	SS	df	MS	
12	Treatment (between columns)	25.62	2	12.81	
13	Residual (within columns)	0.0006000	6	0.0001000	
14	Total	25.62	8		
15					
16	Dunnett's Multiple Comparison Test	Mean Diff.	q	P value	95% CI of diff
17	Column A vs Column B	2.500	306.2	P < 0.01	2.477 to 2.523
18	Column A vs Column C	4.100	502.1	P < 0.01	4.077 to 4.123

Table 9: Micromeritic properties of blend containing metoprolol tartrate and calcium starch prepared using corn starch

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio (%)
F6	0.63± 0.21	0.71± 0.19	11.26±1.21	1.12±0.02
F7	0.67±0.12	0.74±0.09	9.45±1.63	1.23±0.05
F8	0.66±0.17	0.70±0.24	5.71±1.47	1.09±0.03

Comparative metoprolol release profiles observed from the tablets formulated with different types of calcium starch

The formulations that are prepared with calcium starch from different sources and in different ratios showed different rates of drug release. The drug release observed from the formulations that are prepared using calcium starch prepared from potato Starch in different ratios is shown in Figure 19. The drug release was found to be dependent on the

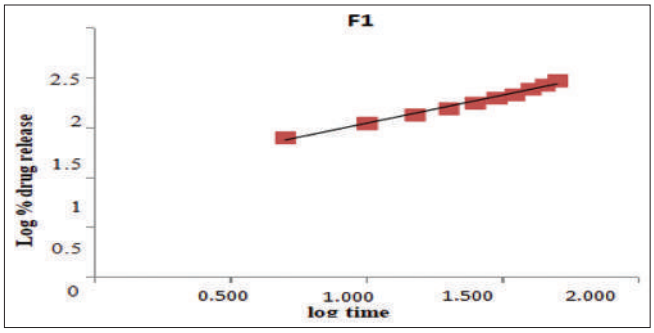


Figure 12: Peppas plots observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using starch

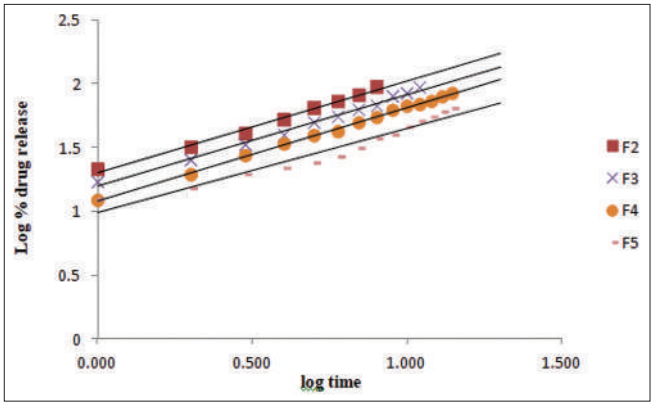


Figure 13: Peppas plots observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using potato starch

Table 10: Physical characters of metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using corn starch

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Average weight (mg)	Friability (%)	Drug content (%)
F6	4.12±0.51	4.3±0.05	217±0.05	0.72±0.03	97.1±0.4
F7	3.93±0.17	3.9±0.07	316±0.03	0.76±0.07	96.5±0.6
F8	4.26±0.31	4.4±0.03	417±0.07	0.81±0.04	97.3±0.3

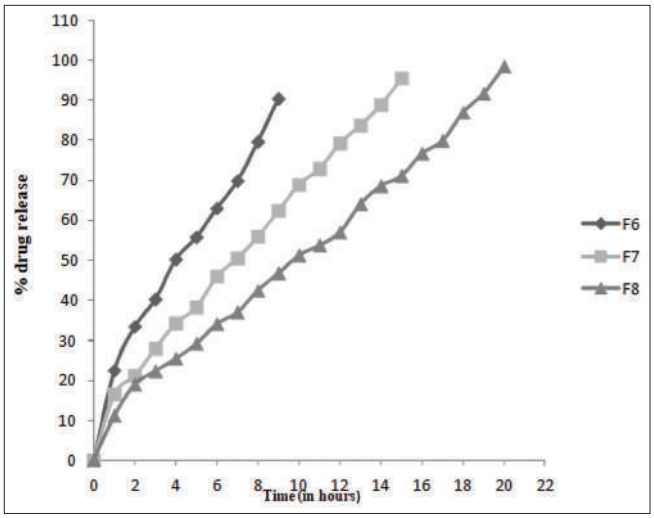


Figure 14: *In vitro* release profiles observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using corn starch

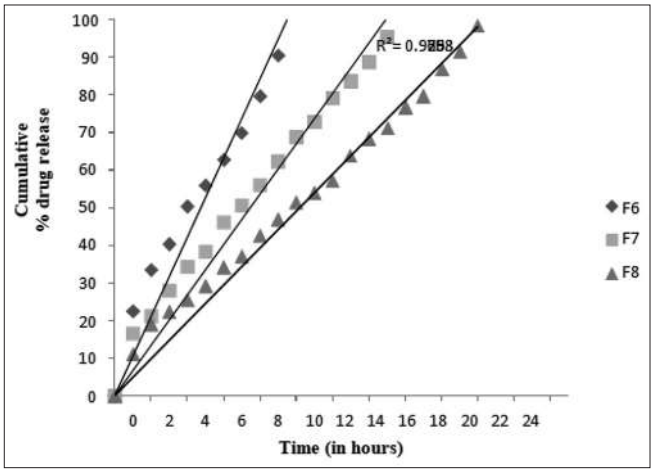


Figure 15: Zero-order plots observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using corn starch

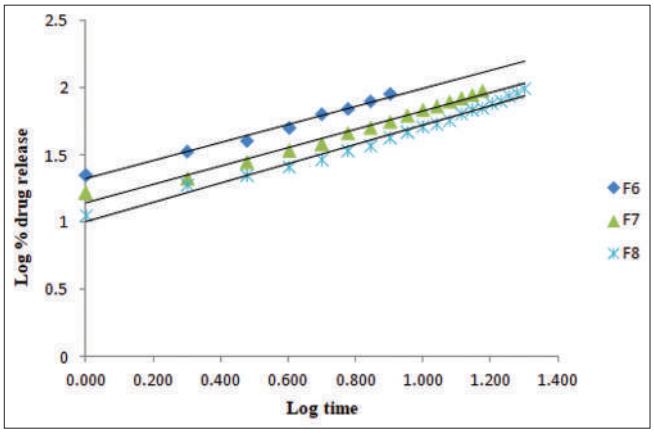


Figure 16: Peppas plots observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using corn starch

Table 11: *In vitro* release observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using corn starch

Time (hours)	% drug release		
	F6	F7	F8
0	0	0	0
1	22.38±1.93	16.44±2.68	11.08±3.09
2	33.33±3.04	21.1±1.21	18.87±2.17
3	40.18±2.27	27.83±1.70	22.25±2.33
4	50.15±2.34	34.19±2.72	25.36±2.28
5	62.92±1.40	38.15±2.80	29.09±3.78
6	69.76±1.46	45.91±1.90	34.01±1.57
7	79.56±2.53	50.42±2.93	36.95±2.50
8	90.33±1.56	55.83±3.79	42.38±1.77
9		62.31±1.56	46.7±2.20
10		68.85±2.41	51.2±2.78
11		72.83±2.37	53.72±3.01
12		79.17± 2.64	56.98±2.95
13		83.69±3.16	64.03±2.77
14		88.82±1.69	68.55±2.47
15		95.44±2.42	71.07±1.95
16			76.65±1.32
17			79.82±1.61
18			86.93±1.86
19			91.64±2.97
20			98.85±2.91

amount of calcium starch present in the formulation. The drug release was found to be reduced with the concentration of calcium starch.

F2 (1:1)	F3(1:2)	F4(1:3)	F5(1:4)
8 hrs-94.37	11hrs-93.6%	16hrs-96.96%	20 hrs-97.41%

The formulations that are prepared with calcium starch from different sources and in different ratios showed different rates of drug release. The drug release observed from the formulations that are prepared using Calcium starch prepared from Corn Starch in different ratios is shown in Figure 20. The drug release was found to be dependent on the amount of calcium starch present in the formulation. The drug release was found to be reduced with the concentration of calcium starch.

F6(1:1)	F7(1:2)	F8(1:3)
9hrs-90.33%	15hrs-95.44%	20hrs-98.42%

The formulations that are prepared with calcium starch from different sources and in different ratios showed different rates of drug release. The drug

Table 12: Release kinetics observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using corn starch

Formulation code	Correlation coefficient(r) value					T50 (h)	f_2
	Zero order	First order	Higuchi	Peppas	Release rate constant k_0 (mg/h)		
F6	0.9624	0.949	0.9828	0.9953	10.54	4.7	33.4
F7	0.9825	0.9239	0.9925	0.9761	6.7004	7.5	52.7
F8	0.9899	0.8377	0.9496	0.9924	4.9087	10.2	58.32

Table 13: ANOVA for formulations of metoprolol tartrate and calcium starch (corn)

	Parameter	A Value Y	B Data Set-B Y	C Data Set-C Y	D Data Set-D Y
1	Table Analyzed				
2	Data 1				
3	One-way analysis of variance				
4	P value	P<0.0001			
5	P value summary	***			
6	Are means signif. different? (P < 0.05)	Yes			
7	Number of groups	3			
8	F	249000			
9	R squared	1.000			
10					
11	ANOVA Table	SS	df	MS	
12	Treatment (between columns)	49.80	2	24.90	
13	Residual (within columns)	0.0006000	6	0.0001000	
14	Total	49.80	8		
15					
16	Dunnett's Multiple Comparison Test	Mean Diff.	q	P value	95% CI of diff
17	Column A vs Column B	3.840	470.3	P < 0.01	3.817 to 3.863
18	Column A vs Column C	5.640	690.8	P < 0.01	5.617 to 5.663

Table 14: Micromeritic properties of blend containing metoprolol tartrate and calcium starch prepared using rice starch

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio (%)
F9	0.55±0.15	0.64±0.12	14.06±1.13	1.16±0.05
F10	0.54±0.26	0.62±0.24	12.90±1.09	1.14±0.02
F11	0.59±0.18	0.67±0.17	11.94±1.29	1.13±0.04

release observed from the formulations that are prepared using calcium starch prepared from rice starch in different ratios is shown in Figure 21. The drug release was found to be dependent on the amount of calcium starch present in the formulation. The drug release was found to be reduced with the concentration of calcium starch.

F9 (1:1)	F10 (1:2)	F11 (1:3)
10 h-89.72%	15 h-97.07%	20 h-98.85%

The formulations showed maximum drug release at same drug and polymer ratio [Figure 22].

F4	F8	F11
96.96%	98.42%	98.85%

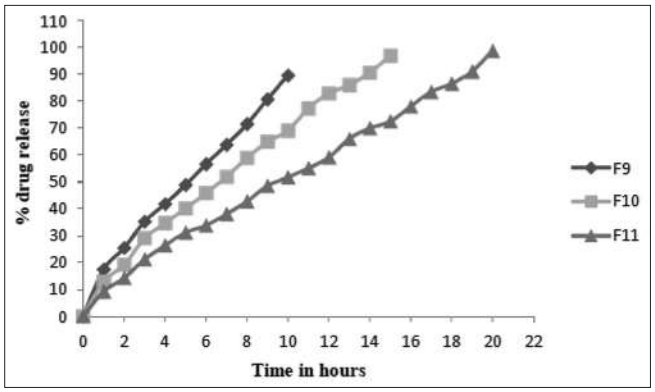


Figure 17: *In vitro* release profiles observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using rice starch

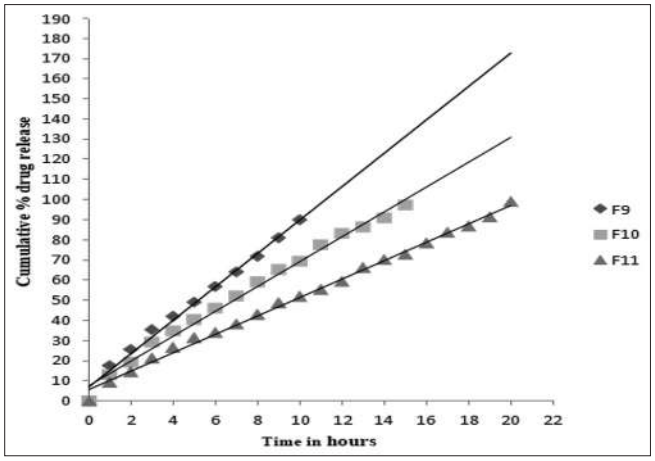


Figure 18: Zero-order plots observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using rice starch

To compare the effect of the source of calcium starch on drug release, the formulations prepared with calcium starch obtained from three different sources potato, corn, and rice starches by employing drug: polymer ratio 1:3 were subjected to drug release studies and the data are presented in Table 6.32 and Figure 23. The drug release followed zero-order and the concerned graph is presented in Figure 24. The mechanism of drug release was found to be the combination of diffusion

Table 15: Physical characters of metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using rice starch

Formulation code	Hardness (kg/cm²)	Thickness (mm)	Average weight (mg)	Friability (%)	Drug content (%)
F9	4.3± 0.19	4.1± 0.03	214.2± 0.05	0.67±0.05	96.7±0.4
F10	4.06± 0.23	3.9± 0.06	316.4± 0.07	0.71±0.09	98.6±0.7
F11	4.23± 0.17	4.3± 0.07	416.3± 0.03	0.65±0.03	98.4±0.3

Table 16: *In vitro* release observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using rice starch

Time (hours)	% drug release		
	F9	F10	F11
0	0	0	0
1	17.45±1.25	12.96±2.18	9.19±3.02
2	25.45±2.41	19.18±3.11	14.36±2.34
3	35.27±2.79	29.08±2.41	21.17±1.81
4	41.85±3.11	34.73±3.13	26.45±2.25
5	48.93±1.14	40.25±2.23	31.2±2.36
6	56.66±2.34	45.9±3.53	33.83±3.09
7	63.87±1.71	51.99±1.93	38.07±1.95
8	71.59±2.45	58.97±3.73	42.78±2.38
9	80.83±1.97	65.09±2.84	48.56±1.70
10	89.72±3.21	69.19±3.79	51.77±2.72
11		77.39±2.47	55.17±1.98
12		83.05±3.67	59.16±3.64
13		86.15±2.44	66.1±1.77
14		90.72±1.55	70.05±2.56
15		97.07±2.45	72.59±2.82
16			78.19±1.65
17			83.55±3.46
18			86.63±2.42
19			91.19±1.70
20			98.85±2.53

and erosion as the exponential coefficient value observed from Peppas plot Figure 25 was found to be in between 0.5 and 1 (0.73, 0.72, 0.79). The drug release rate observed from these formulations was treated statistically with one-way ANOVA and the results are presented in Table 19 and these results indicated that the differences in drug release rate were found be statistically significant. The drug release observed from the formulations prepared with calcium starch obtained from potato starch was found to be relatively slow compared with the other formulations. However, the drug release observed from the formulations prepared with calcium starch obtained from corn starch and rice starch was not significant statistically

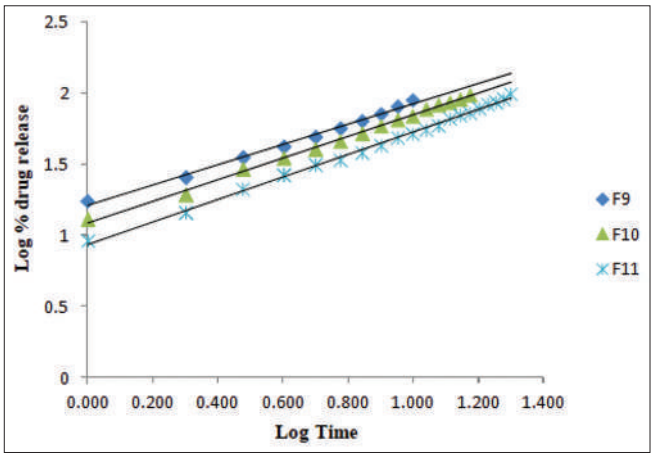


Figure 19: Peppas plots observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using rice starch

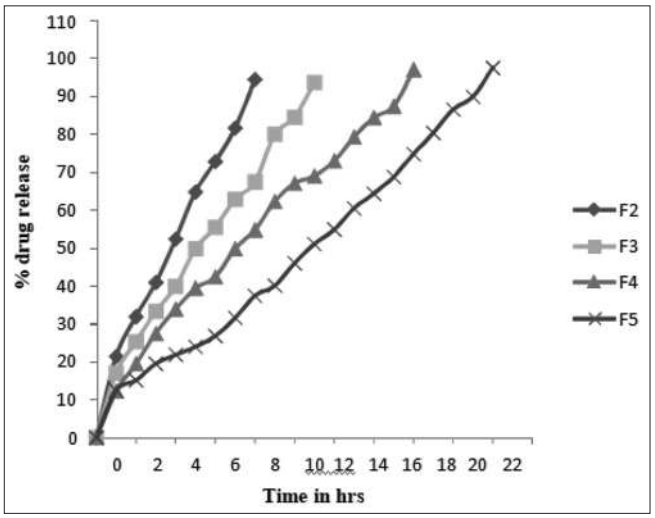


Figure 20: Comparative metoprolol release profiles observed from the tablets formulated with different ratios of calcium starch (potato). Drug: polymer ratio (potato calcium starch): F2 (1:1), F3 (1:2), F4 (1:3), F5 (1:4)

and hence these two starches are more suitable for formulation of sustained-release formulations.

SUMMARY

Metoprolol tartrate in oral conventional dosage form has the dosage regime of 2 times a day due to

Table 17: Release kinetics observed from metoprolol tartrate tablets formulated with different ratios of calcium starch prepared using rice starch

Formulation code	Correlation coefficient(r)value					T50 (h)	f2
	Zero order	First order	Higuchi	Peppas	Release rate constant k_0 (mg/h)		
F9	0.9852	0.9481	0.9673	0.9963	9.2752	5.4	40.95
F10	0.986	0.9121	0.9644	0.9984	6.9032	7.2	95
F11	0.9926	0.7153	0.9501	0.9982	4.9953	10	58.7

Table 18: ANOVA for formulations of metoprolol tartrate and calcium starch (rice)

	Parameter	A Value Y	B Data Set-B Y	C Data Set-C Y	D Data Set-D Y
1	Table Analyzed				
2	Data 2				
3	One-way analysis of variance				
4	P value	P<0.0001			
5	P value summary	***			
6	Are means signif. different? (P < 0.05)	Yes			
7	Number of groups	3			
8	F	137900			
9	R squared	1.000			
10					
11	ANOVA Table	SS	df	MS	
12	Treatment (between columns)	27.57	2	13.79	
13	Residual (within columns)	0.0006000	6	0.0001000	
14	Total	27.58	8		
15					
16	Dunnett's Multiple Comparison Test	Mean Diff.	q	P value	95% CI of diff
17	Column A vs Column B	2.360	289.0	P < 0.01	2.337 to 2.383
18	Column A vs Column C	4.280	524.2	P < 0.01	4.257 to 4.303

Table 19: Statistical analysis of comparative metoprolol release profiles observed from the tablets formulated with different types of calcium starch till desired time

	Parameter	A Value Y	B Data Set-B Y	C Data Set-C Y	D Data Set-D Y
1	Table Analyzed				
2	Data 1				
3	One-way analysis of variance				
4	P value	P<0.0001			
5	P value summary	***			
6	Are means signif. different? (P < 0.05)	Yes			
7	Number of groups	3			
8	F	18820			
9	R squared	0.9998			
10					
11	ANOVA Table	SS	df	MS	
12	Treatment (between columns)	3.763	2	1.882	
13	Residual (within columns)	0.0006000	6	0.0001000	
14	Total	3.764	8		
15					
16	Dunnett's Multiple Comparison Test	Mean Diff.	q	P value	95% CI of diff
17	Column A vs Column B	1.410	172.7	P < 0.01	1.387 to 1.433
18	Column A vs Column C	1.330	162.9	P < 0.01	1.307 to 1.353

a short elimination half-life of 3–4 h. The extended-release single unit dosage form has the demerits of all and nothing effect, person to person variability,

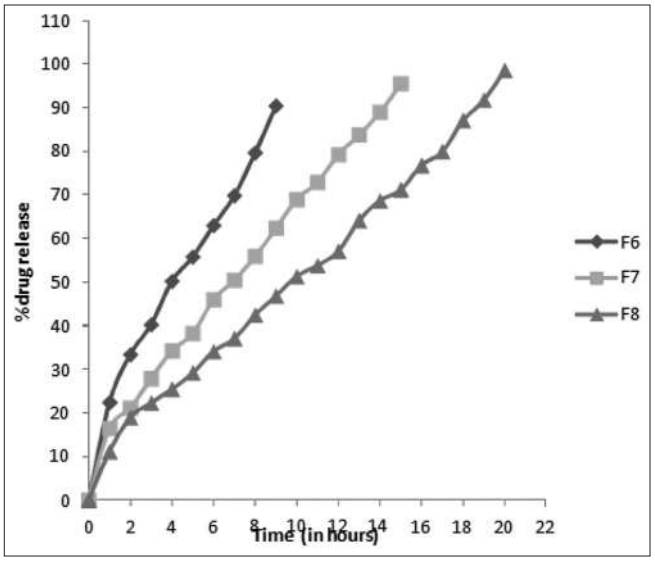


Figure 21: Comparative metoprolol release profiles observed from the tablets formulated with different ratios of calcium starch (corn). Drug: polymer ratio (corn calcium starch) F6 (1:1), F7 (1:2), F8 (1:3)

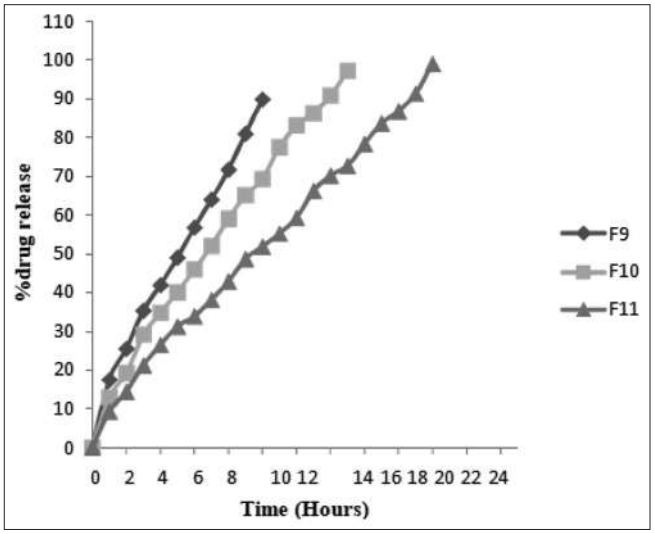


Figure 22: Comparative metoprolol release profiles observed from the tablets formulated with different ratios of calcium starch (rice). Drug: polymer ratio (rice calcium starch) F9 (1:1), F10 (1:2), F11 (1:3)

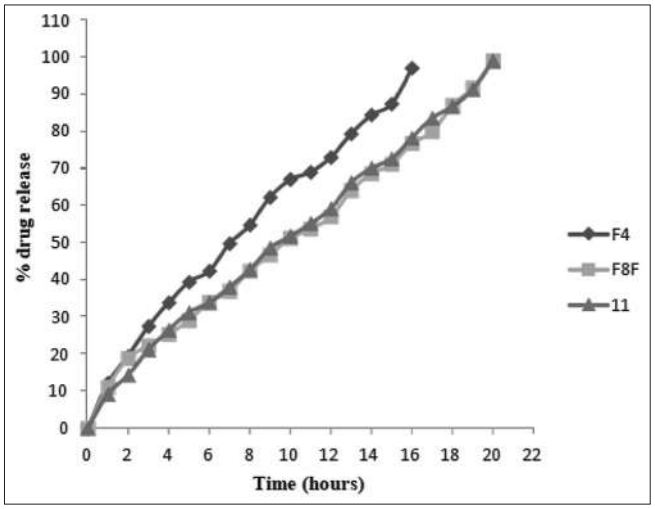


Figure 23: Plots for comparative metoprolol release profiles observed from the tablets formulated with different types of calcium starch

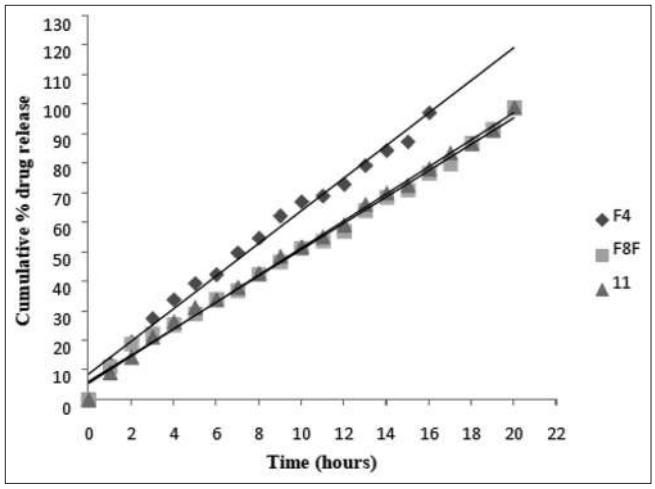


Figure 24: Zero-order plots for comparative metoprolol release profiles observed from the tablets formulated with different types of calcium starch

and non-uniform drug release. These complaints certainly can be overcome by the sustained release multiunit dosage form like tablets. The principal aim of the investigation undertaken was to develop a Multi-Particulate Drug Delivery System for anti-hypertensive drug metoprolol tartrate. In the present investigation, sustained-release tablets were prepared using wet granulation technique using modified starch called calcium starch prepared using different types of starches such as potato starch, corn starch and rice starch. The drug and the modified starches were subjected to IR-spectra studies to notice the drug excipient interactions (if any). The resulting IR spectral data

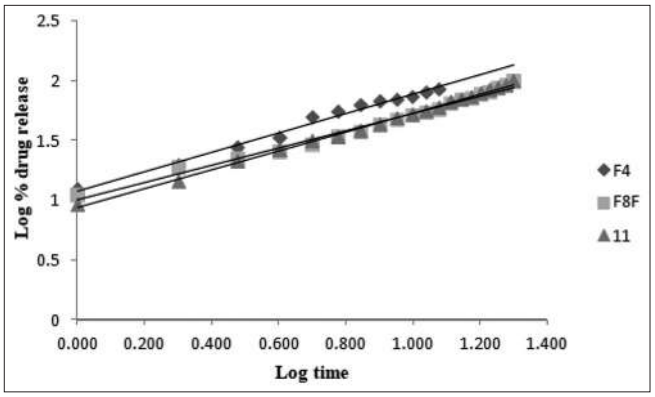


Figure 25: Peppas plots for comparative metoprolol release profiles observed from the tablets formulated with different types of calcium starch

are presented in Figures 5–7. The principle peaks observed with the metoprolol tartrate were also noticed with the blends and hence these results clearly demonstrated that the metoprolol tartrate is compatible with modified starch and the blends can be used to develop metoprolol tartrate sustained-release tablets. The granules of metoprolol tartrate were prepared with the starch and modified starch (potato) and the granules having a mess size of 24 were evaluated for micromeritic properties. The observed result is presented in Table 4 and these results (Hausner's ratio and Carr's index) indicated that the material having good flow property and as such they can be used to formulate sustain release tablets.

All the formulated tablets (F1 to F5) were evaluated for thickness, hardness, friability, weight variation, and drug content and the results are presented in Table 5. The formulated tablets satisfied all the quality control requirements and found to be within limits. The formulated tablets (F1 to F5) were subjected to *in vitro* drug release studies and resulting data are presented in Tables 6 and 7 and Figures 6 and 7. In order to assess the kinetic release of the formulations, it was subjected to various kinetic release models, as summarized in Table 6.7. The drug release followed zero-order kinetics, as the graph drawn between amount of drug release versus time was found to be linear [Figures 9 and 10]. The release rate constant and time required to get 50% of drug release were calculated and results were depicted in Table 6.7.

Korsmeyer and Peppas equation, that is,

$Q_t/Q_\infty = K_K t^n$, where Q_t/Q_∞ is the fraction released by the drug at time t, K_K is a constant incorporating structural and geometric characteristic, and n is their lease exponent characteristic for the drug transport mechanism. Table 6.7 summarizes the release exponent "n" value for different release kinetics reported in literature. The observed correlation coefficient r values were reported in Table 6.7. The release data observed from these formulations were compared with the theoretical release profiles that were given in USP. The observed similarity factors were reported in Table 6.7. The similarity factor of tablets formulated with starch (7.8), modified starch (potato) with 1:1 drug: calcium starch ratio (28.35), 1:2 drugs: calcium starch ratio (44.05) was <50, where the tablets formulated with 1:3 drug: calcium starch ratio (56.73) and 1:4 drug: calcium starch ratio (52.23) have similarity factor more than 50. The value of n [Table 6.7] as estimated by linear regression of log Q_t/Q_∞ versus log t of formulations (F2, F3, F4, F5) 0.71, 0.71, 0.73, and 0.74 was indicated that drug release from tablets followed Anomalous (non-Fickian) diffusion. To ascertain the mechanism of drug release, the data are fitted in Peppas plots [Figures 11 and 12]. The release rate constant of metoprolol tartrate observed from tablets prepared with modified starches are treated statistically with one-way ANOVAs followed by Dunnett's method was reported in Table 8. From the observed results, it was found that the formulation F2 is significant when compared with other formulations (F3 to F5). The granules of metoprolol tartrate were prepared with the starch and modified starch (corn) and the granules having a mess size of 24 were evaluated for micromeritic properties. The observed result is presented in Table 9 and these results (Hausner's ratio and Carr's index) indicated that the material having good flow property and as such they can be used to formulate sustained-release tablets. All the formulated tablets (F6 to F8) were evaluated for thickness, hardness, friability, weight variation and drug content, and the results are presented in Table 10. The formulated tablets satisfied all the quality control requirements and found to be within limits. To assess the kinetic release of the formulations, it was subjected to various kinetic release models, as summarized in Table 12. The drug release followed zero-order kinetics, as the graph drawn between amount of drug release versus time was found to be linear [Figure 14].

The formulated tablets (F6 to F8) were subjected to *in vitro* drug release studies and resulting data are presented in Table 11 and Figure 13. The release rate constant and time required to get 50% of drug release were calculated and results were depicted in Table 12. Korsmeyer and Peppas equation, that is, $Q_t/Q_\infty = K_K t^n$, where Q_t/Q_∞ is the fraction released by the drug at time t, K_K is a constant incorporating structural and geometric characteristic, and n is their lease exponent characteristic for the drug transport mechanism. Table 12 summarizes the release exponent "n" value for different release kinetics reported in literature. The observed correlation coefficient r values were reported in Table 12. The release data observed that from these formulations were compared with the theoretical release profiles that were given in USP. The observed similarity factors were reported in Table 12. The similarity factor of tablets formulated with modified starch (corn) with 1:1 drug: calcium starch ratio (33.4) was <50, where the tablets formulated with 1:2 drug: calcium starch ratio (52.7) and 1:3 drug: calcium starch ratio (58.32) have similarity factor more than 50.

The value of n [Table 12] as estimated by linear regression of log Q_t/Q_∞ versus log t of formulations (F6, F7, F8) 0.61, 0.68, and 0.72 was indicated that drug release from tablets followed Anomalous (non-Fickian) diffusion. To ascertain the mechanism of drug release, the data are fitted in Peppas plots [Figure 15]. The release rate constant of metoprolol tartrate observed from tablets prepared with modified starches are treated statistically with one-way ANOVA followed by Dunnett's method was reported in Table 13. From the observed results, it was found that the formulation F6 is significant when compared with other formulations (F7 and F8). The granules of metoprolol tartrate were prepared with the starch and modified starch (rice) and the granules having a mess size of 24 were evaluated for micromeritic properties. The observed result is presented in Table 14 and these results (Hausner's ratio and Carr's index) indicated

that the material having good flow property and as such they can be used to formulate sustain release tablets. All the formulated tablets (F9 to F11) were evaluated for thickness, hardness, friability, weight variation, and drug content and the results are presented in Table 15. The formulated tablets satisfied all the quality control requirements and found to be within limits. The formulated tablets (F9 to F11) were subjected to *in vitro* drug release studies and resulting data are presented in Table 16 and Figure 16. To assess the kinetic release of the formulations, it was subjected to various kinetic release models, as summarized in Table 17. The drug release followed zero-order kinetics, as the graph drawn between amount of drug release versus time was found to be linear [Figure 17]. The release rate constant and time required to get 50% of drug release were calculated and results were depicted in Table 17. Korsmeyer and Peppas equation, that is, $Q_t/Q_\infty = K_K t^n$, where Q_t/Q_∞ is the fraction released by the drug at time t, K_K is a constant incorporating structural and geometric characteristic, and n is their lease exponent characteristic for the drug transport mechanism. Table 17 summarizes the release exponent "n" value for different release kinetics reported in literature. The observed correlation coefficient r values were reported in Table 17. The release data observed from these formulations were compared with the theoretical release profiles that were given in USP. The observed similarity factors were reported in Table 17. The similarity factor of tablets formulated with modified starch (rice) with 1:1 drug: calcium starch ratio (40.95) was <50, where the tablets formulated with 1:2 drug: calcium starch ratio (95), and 1:3 drug: calcium starch ratio (58.7) have similarity factor more than 50. The value of n [Table 17] as estimated by linear regression of log Q_t/Q_∞ versus log t of formulations (F9, F10, F11) 0.71, 0.76, and 0.79 was indicated that drug release from tablets followed Anomalous (non-Fickian) diffusion. In order to ascertain the mechanism of drug release, the data are fitted in Peppas plots [Figure 18]. The release rate constant of metoprolol tartrate observed from tablets prepared with modified starches are treated statistically with one-way ANOVAs followed by Dunnett's method was reported in Table 18. From the observed results, it was found that the formulation F9 is significant when compared with other formulations (F10 and F11).

CONCLUSION

The following conclusions were drawn from experimental results:

- The micromeritic properties of Metoprolol tartrate granules formulated with starch, modified, and different concentrations of modified starch exhibited good flow characteristics
- The drug and the modified starch blends were subjected to IR-spectra studies to notice the drug excipient interactions (if any). The principle peaks observed with the metoprolol tartrate were also noticed with the blends and hence these results clearly demonstrated that the metoprolol is compatible with modified starches and the blends can be used to develop metoprolol tartrate sustained-release tablets
- All the formulated tablets (F1 to F11) were evaluated for thickness, hardness, friability, weight variation, and drug content. The formulated tablets satisfied all the quality control requirements and found to be within limits
- All the formulated tablets (F1 to F11) were subjected to *in vitro* drug release studies. The drug release from all the formulations with starch and modified starch followed zero-order release kinetics.
- The value of "n" as estimated for calcium starch(potato) by linear regression of log Q_t/Q_∞ versus log t of formulations (F2, F3, F4, F5) was 0.71, 0.71, 0.73, and 0.74 indicated that drug release from tablets followed Anomalous (non-Fickian) diffusion
- The value of "n" as estimated for calcium starch (corn) by linear regression of log Q_t/Q_∞ versus log t of formulations (F6, F7, F8) was 0.61, 0.68, and 0.72 indicated that drug release from tablets followed Anomalous (non-Fickian) diffusion

- The value of "n" as estimated for calcium starch(rice) by linear regression of log Q_t/Q_∞ versus log t of formulations (F9, F10, F11) was 0.71, 0.76, and 0.79 indicated that drug release from tablets followed Anomalous (non-Fickian) diffusion
- The release data observed from all the formulated tablets (F2 to F11) were compared with the theoretical release profiles given in USP. From the observed results, the formulations F5, F8, F11 have similarity factor greater than 50 and satisfied all the requirements.

Recommendations

The following recommendations are suggested for the continuation of this research work:

Selection of packing materials

Suitable packing material may be selected to assure good stability to the optimized formulation.

Stability studies

The stability studies can be conducted on the Metoprolol tartrate formulated with calcium starch as per ICH guidelines.

Pharmacokinetic and pharmacodynamics studies

The efficiency of this formulation can be determined by conducting pharmacokinetic and pharmacodynamics studies on suitable animal models.

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