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Formulation and Evaluation of Desvenlafoxacine Succinate Hydrogel

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A B S T R A C T

Corn starch is abundantly available in nature with the help of it we can prepare controlled release dosage form. Starch hydrogel is the current area of research for developing various controlled release dosage forms. Starch hydrogels are prepared easily with the normally available ingredients. The major advantage of hydrogel is the control release behavior up to 24 hrs. In the present study corn starch hydrogel was prepared by using Glutaraldehyde reagent and Poly Vinyl Alcohol they formed hydrogel was able up to control the drug release up to 24 hrs. The swelling behavior and drug release studies were performed and the dissolution data was fit into various kinetic models which showed drug release mechanism was of non fickian diffusion type.

Keywords: corn starch, hydrogel, glutaraldehyde, Poly Vinyl Alcohol

A R T I C L E I N F O

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1. Introduction

The hydrogels, since their discovery by Wichterle and Lim in 1960[1] of poly (2-hydroxyethyl methacrylate)[1], have been of great interest to biomedical scientists. The terms gels and hydrogels are used interchangeably by food and biomaterials scientists to describe polymeric cross-linked network structures. Gels are defined as a substantially dilute cross-linked system, and are categorized principally as weak or strong depending on their flow behaviour in steady-state. Edible gels are used widely in the food industry and mainly refer to gelling polysaccharides (i.e.

hydrocolloids). The term hydrogel describes three-dimensional network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant amount of water (Rosiak & Yoshii, 1999).

The hydrogel structure is created by the hydrophilic groups or domains present in a polymeric network upon the hydration in an aqueous environment. Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids, and retaining a large amount of fluids in the swollen state[2]. Their ability to absorb water is due to the presence of hydrophilic groups such as –OH,–CONH, COOH, and –SOH. The water content in hydrogels affects different properties like permeability, mechanical properties, surface properties, and biocompatibility[3]. Hydrogels have similar physical properties as that of living tissue, and this similarity is due to the high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids[4]. The ability of molecules of different size to diffuse into (drug loading and out (release drug) of hydrogels, permit the use of hydrogels as delivery systems. Since hydrogels have high permeability for water soluble drugs and proteins the most common mechanism of drug release in the hydrogel system, is diffusion. Factors like polymer composition, water content, crosslinking density, and crystallinity, can be used to control the release rate and release mechanism from hydrogels[5].

Types of Hydrogels

Hydrogels, based on their nature, can be classified as

- pH sensitive,
- temperature sensitive,
- Enzyme sensitive and electrical sensitive.

pH sensitive

Hydrogels can be neutral or ionic in nature. The anionic hydrogels contain negatively charged moieties, cationic networks contain positively charged moieties, and neutral networks contain and nagatively charged moieties. In neutral hydrogels, the driving force for swelling arises from the water-polymer thermodynamic mixing contributions, and elastic polymer contributions. In ionic hydrogels, the swelling is due to the previous two contributions, as well as ionic interactions between charged polymer and free ions[6]. The presence of ionizable functional groups like carboxylic acid, sulfonic acid or amine groups, renders the polymer more hydrophilic, and results in high water uptake In the case of anionic polymeric network containing carboxylic or sulphonic acid groups, ionization takes place, as the pH of the external swelling medium rises above the pK of that ionizable moiety. The dynamic swelling change of the anionic hydrogels can be used in the design of intelligent controlled release devices for site-specific drug delivery of therapeutic proteins to large intestine, where the biological activity of the proteins is prolonged. The change in the pH of the external environment will act as stimulus and the response to the stimulus is the change in swelling properties of the hydrogels, causing the release of the protein.

Bettini et al[7] prepared anionic copolymer of methyl methacrylate and 2 – hydroxyethyl methacrylate by bulk polymerization, using ethylene glycol dimethacrylate as cross linking agent. The prepared pH sensitive delivery system showed increased swelling above the pK (5.9) of methyl methacrylate. The drug release was relaxation controlled, since the swelling of glassy polymer was accompanied by chain relaxation process. Hydrogels of poly (acrylic acid) (PAA), and poly (acry1ic acid-co-2-hydroxyethyl methacrylate) [P(AA-co-HEMA)] hydrogels, were synthesized by Ended and Peppas[8] with varying degree of hydrophilicity and cross linking density, and were studied as potential bioadhesive controlled-release dosage forms. Equilibrium and dynamic swelling studies were carried out to determine the polymer mesh size and molecular weight between crosslink's of the hydrogels, in the ionized and nonionized states. The PAA hydrogel mesh sizes ranged from 100 to 400 Å, over pH values of 3-7, whereas the p(AA-co-HEMA) hydrogel mesh sizes were between 13 and 140 Å. These results demonstrated the significance of the swelling medium pH on the hydrated state of the polymers, related to cross linking or copolymerization composition.

The polymer morphology was modified by changing the cross-linking agent (TEGDMA) concentration (0-0.95%). The swelling rates and swelling extent increased at a steady state, with decreasing cross-linking agent concentration. The matrices without cross-linking agent were stable in water, and did not dissolve in water for an extended period of few months. Also, it was observed that physically cross-linked hydrogel showed faster insulin release rates, than chemically cross-linked hydrogel. The *in vivo* experiment with physically cross-linked hydrogel showed significant reduction in blood glucose levels from 400 mg/dl to100- 200 mg/dl after 2.5 h and to 50-120 mg/dl after 6.5h. Electric current can also be used as an environmental signal to induce responses of hydrogels. Hydrogels, sensitive to electric current, are usually made of poly electrolytes. An electric field as an external stimulus has advantages, such as the availability of equipment, which allows precise control with regards to the magnitude of current, duration of electric pulses, intervals between pulses, etc. It has been demonstrated that, four distinct electrochemical and electromechanical mechanisms exists for selective controlled transport of proteins and neutral solutes across hydrogel membranes:

- Electrically and chemically induced swelling of a membrane to alter the effective pore size and permeability
- Electrophoretic augmentation of solute flux within a membrane
- Electroosmotic augmentation of solute flux within the membrane
- Electrostatic partitioning of charged solutes into charged membranes[18] Sahawata *et al*[19].

Studied microparticles of sodium salt poly (acrylic acid) as an electroresponsive delivery system using pilocarpine as model drug. The microparticles showed 96% volume change within 50 s of application of a d.c. of 0.3 mA cm. The deswelling occurred due to diffusion of mobile cations away from the carboxylate ions, under the influence of an

electric field gradient. The carboxylate anions remain undissociated under this condition, and leads to the constriction of gel. The pilocarpine release observed was, 9.8×10 mol dm when d.c. was applied, and when switched off, the release decreased to 1.8 x 10^{-7} mol dm^{-3} s^{-1}. The electrical behaviour of the interpenetrating polymer network (IPN) hydrogel composed of sodium alginate (SA) and poly (diallyldimethyl ammonium chloride) (PDADMAC) was studied by Kim *et al*[20].

The SA/ PDADMAC IPN hydrogel exhibited pH and electrolyte concentration sensitive behavior. When an electric field is applied to a strip of the SA/PDADMAC IPN hydrogel in an aqueous HCl solution, the gel showed significant and quick bending toward the cathode. The bending angle measured was 90°, 82°, 52°, and 27° at 15, 10, 7 and 5 V respectively, at a constant HCl concentration. It was concluded that the deformation of a polymer hydrogel under an electric field was due to the voltage-induced motion of ions, and the concomitant expansion of one side of the polymer and the contraction of the other side of the polymer. Kim *et al*[21].studied interpenetrating polymer networks (IPN) hydrogels of poly(vinyl alcohol) (PVA), and hyaluronic acid (HA). When swollen, IPN was placed between a pair of electrodes, and an electric field applied, it exhibited bending behavior. The equilibrium bending angle (EBA) of the PVA/HA IPN showed an apparent peak (74°) in a 0.25M aqueous NaCl solution. The bending degree increased with increasing NaCl solution concentration, with concentrations <0.25 M. However, the bending degree decreased with NaCl solution concentrations >0.25 M. The bending angle measured was 72°, 58°, 38°, and 22° at 15, 10, 7, 5 V respectively, at a constant NaCl concentration.

Temperature sensitive

Thermo sensitive hydrogels are one of the widely studied responsive polymer systems. The thermosensitive polymers are characterized by the presence of hydrophobic groups, such as methyl, ethyl, and propyl groups. The most widely studied temperature sensitive polymer is poly(N-isopropylacrylamide) P(NIPAAm). P(NIPAAm) is a non-biodegradable polymer with a LCST 32^0C in water and cross linked gels of this material collapse around this temperature[22]. Pluronics or Poloxomers are the commercially available poly (ethylene oxide) (PEO) and poly(propylene oxide) (PPO). These copolymers show phase change from sol- gel around body temperature, and are used as injectable implants. Temperature sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels[23]. Certain hydrogels formed by IPNs show swelling at high temperature, and shrinking at low temperature. IPNs of poly(acrylic acid) and polyacrylamide (PAAm) or poly poly(acrylamide–co-butyl methacrylate), have positive temperature dependence of swelling. Such types of hydrogels are called positively thermosensitive hydrogels. The negatively thermosensitive hydrogels include P (NIPAAm–co-BMA) hydrogels[24] and inter-penetrating polymer networks (IPNs) of P (NIPAAm) and poly (tetramethyl eneether glycol) (PTMEG). These type of hydrogels swell when the temperature is decreased, and deswell when the temperature is increased. The on-off release profile of drugs from the matrices was explained by the formation of a dense, less permeable surface layer of gel, described as a skin-type barrier. The former allows the gel to exhibit temperature sensitivity and the latter gives the gel a pH-sensitivity. It was found that the crosslinked co-polymer gel of NIPAAm/ DMAPMAAm in the molar ratio of 97:3, demonstrated a pH-sensitivity around pH 7.4 as well as a temperature sensitivity around 37°. The insulin release profile exhibited Fickian diffusion at 32°, and showed a near zero-order release at 42°, while a two-stage release profile was observed at 37°. Erbil *et al*[28]. *have* synthesized and characterised poly(dimethyl siloxane)/ poly(N-isopropyl acrylamide) PDMS/P(NIPAAm) semi-interpenetrating networks. The phase morphologies was characterized by FTIR, DSC, and SEM. Semi-IPNs exhibited phase transition temperatures higher than glass-6-aminohexanoylamino) or 3,32,5,52-tetrabromo-4, transition temperatures of their respective homopolymers, suggesting a heterophase morphology, and only physical entanglement between the P(NIPAAm) network and linear PDMS. The results suggested that these materials can be developed as ophthalmic biomaterials, or for controlled drug-release applications. The diffusional characteristics for P (NIPAA m) gel for glucose and insulin with changing temperature have been investigated by Andersson and others[30]. The gel was a critical one which means that small changes in the environment influenced the gel volume considerably. The effective diffusion coefficients for the solutes glucose insulin were determined below the critical temperature: 10, 20 and 30°. The effective diffusion coefficient for glucose increases from 2.7x10^{-10} to 4.7x10^{-10} m^2/s and for insuin effective diffusion coefficient increased from 4.4x10^{-10} to 5.9x10^{-10} m^2/s when the temperature was changed from 10 to 30°.

Enzyme sensitive hydrogels

Enzyme sensitive hydrogels are mainly used in the targeting of drugs to colon. The colon-specificity is achieved due to the presence of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure. When hydrogels pass through GI tract, the swelling capacity increases as the pH increases, due to the presence of pH sensitive polymers, swelling being highest around pH 7.4. Upon arrival in the colon, the hydrogels have reached a degree of swelling, that makes the cross-links accessible to the enzymes (azoreductase) or mediators. Subsequently, the hydrogel network is progressively degraded via the cleavage of the cross-links, and the drug entrapped is thus released[31]. The hydrogels can be obtained by cross- linking polymerization of *N*-substituted (meth) acrylamides, *N*-*tert*-butyl acryl amide and acrylic acid, with 4,42di (methacryloylamino) azobenzene, 4, 42-di (*N*- methacryloyl4, 42, 42-tetrakis (methacryloylamino) azobenzene as the cross- linking agents[32].

Starch Hydrogels

Hydrogels of natural polymers, especially polysaccharides, have been used recently because of their unique advantages. Polysaccharides are, in general, non-toxic, biocompatible, biodegradable, and abundant. However if the polysaccharide dissolves in water it cannot form stable

hydrogel. One effective method to avoid these limitations is to combine them into a synthesized polymer blend hydrogels, which is becoming a subject of academic as well as of industrial interest. Hydrogels can be applied as an interface between bone and an implant, as wound dressings, as contact lenses, as blood contact materials and in-controlled release applications for delivery of enzymes, hormones, contraceptives and anticoagulant. Biodegradable polymers such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA) and their respective copolymers have been used in several drug delivery systems. However few attempts have been made to use starch-based polymers in these type of applications; despite being well known that they are biodegradable materials, they have been proposed in several works to be used as biomaterials. Starch is one of the most abundant and cheap polysaccharides. Usually starch includes about 30% amylose (a linear α-(1,4) glucan) and 70% amylopectin (dendritically branched version). Chemically modified starches with improved properties are becoming more and more important in industry application not only because they are low in cost, but mainly because the polysaccharide portion of the product is biodegradable. Chemical modification of starch via graft copolymerization of vinyl monomers onto it has been studied widely in recent years. But only a few studies on starch polymer blend hydrogels have been reported. In this work attempts were made to prepare polyvinyl alcohol (PVA)/starch blend hydrogels by chemical crosslinking technique and to characterize the same. The use of polymers from renewable resources is an environmentally advantageous alternative to synthetic polymers in some applications (Kofuji, Isobe, & Murata, 2009; Rouilly & Rigal, 2002; Thakur et al., 2009). Starch is a well-known, versatile, and inexpensive agricultural material used for a variety of industrial applications. In addition to being a major food item, it is currently used industrially as coatings and sizing in paper, textiles and carpets, as binders and adhesives, as absorbants (Kiatkamjornwong, Chomsaksakul, & Sonsuk, 2000), and as encapsulants (Stephen, 1995; Whistler & BeMiller, 1993) bone replacement implants (Reis & Cunha 1995), bone cements (Reis, Mendes, Cunha, & Bevis, 1997), drug delivery systems (Onofre, Wang, & Mauromoustakos, 2009), and tissue engineering scaffolds (Gomes, Ribeiro, Malafaya, Reis, & Cunha, 2001).

Preparation of Hydrogels:

Several techniques have been reported for the synthesis of hydrogels. The first approach involves copolymerization /cross linking of co-monomers using multifunctional co-monomer, which acts as cross linking agent. The polymerization reaction is initiated by chemical initiator. The polymerization reaction can be carried out in bulk, in solution, or in suspension. The second method involves cross linking of linear polymers by irradiation, or by chemical compounds. The monomers used in the preparation of the ionic polymer network contain an ionizable group, a group that can be ionized, or a group that can undergo a substitution reaction after the polymerization is completed. As a result, hydrogels synthesized contain weakly acidic groups like carboxylic acids, or a weakly basic group like substituted amines or a strong acidic and basic group like sulfonic acids, and quaternary ammonium compounds. Some of the commonly used crosslinking agents include N, N glycol dimethacrylate

Solution polymerization/cross linking:

In solution, co-polymerization/cross linking reactions, and ionic or neutral monomers are mixed with the multifunctional cross linking agent. The polymerization is initiated thermally, by UV-light, or by redox initiator system. The presence of solvent serves as heat sink, and minimizes temperature control problems. The prepared hydrogels need to be washed with distilled water to remove the unreacted monomers, cross linking agent and the iniator. The best example is preparation of poly (2-hydroxyl ethyl methacrylate) hydrogels from hydroxyethyl methacrylate, using ethylene glycol dimethacrylate as cross linking agent. Using the above method, a great variety of hydrogels have been synthesized[33]. The hdrogels can be made pH sensitive/ temperature sensitive by incorporating methacrylic acid, methylene bisacrylaminde, di vinyl benzene and ethylene isopropyl arylamide[35] as monomers.

Ionic Monomers Used In Preperation of Hydrogel

- Anionic acidic monomers: Acrylic acid, methacrylic acid
- Cationic basic monomers: Vinyl pyridine, 2-methacryloylloxy-trimethylammonium chloride.

Neutral Monomers Used In Preperation of Hydrogel

Acrylamide, 2-hydroxyethyl methacrylate

Polyfunctional Cross Linking Monomers for Hydrogel Synthesis: N, N-Methylenebisacrylamide, ethylene glycol dimethacrylate

Suspension polymerization

This method is employed to prepare spherical hydrogel microparticles with size range of 1 µm to 1mm. In suspension polymerization, the monomer solution is dispersed in the non-solvent forming fine droplets, which are stabilized by the addition of stabilizer. The polymerization is initiated by thermal decomposition of free radicals. The prepared microparticles then washed to remove unreacted monomers, crosslinking agent, and initiator. Hydrogel microparticles of poly(vinyl alcohol) and poly(hydroxy ethyl methacrylate) have been prepared by this method.

Polymerization by irradiation:

High energy radiation like gamma and electron beam, have been used to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains. Also, radiolysis of water molecules results in the formation hydroxyl radicals, which also attack the polymer chains resulting in the formation of macro radicals. Recombination of the macroradicals on different chains results in the formation of covalent bonds, and finally a cross linked structure is formed[36]. During radiation, polymerization macro radicals can interact with oxygen, and as a result, radiation is performed in an inert atmosphere using nitrogen or argon gas. Examples of polymers cross linked by radiation method include poly (vinyl alcohol), poly (ethylene glycol) poly poly(acrylic acid) advantage over chemical initiation is the production of relatively pure, residue-free hydrogels.

Chemically crosslinked hydrogels:

Polymers containing functional groups like –OH, – COOH, –NH, are soluble in water. The presence of these functional groups on the polymer chain, can be used to prepare hydrogels by forming covalent linkages between the polymer chains and complementary reactivity, such as amine-carboxylic acid, isocyanate-OH/NH or by Schiff base formation. Gluteraldehyde can be used as a crosslinking agent to prepare hydrogels of polymers containing –OH groups like poly (vinyl alcohol). Also, polymers containing amine groups (albumin, gelatin, polysaccharides) cross linked using gluteraldehyde. Polymers that are water soluble, can be converted to hydrogels, using bis or higher functional crosslinking agents like divinylsulfone, and 1,6-hexanedibromide.The cross linking agents react with the functional groups present on the polymer, via addition reaction. These cross linking agents are highly toxic, and hence unreacted agents have to be extracted. Moreover the reaction has to be carried out in organic solvent, as water can react with the cross linking agent. The drugs have to be loaded after the hydrogels are formed, as a result the release will be typically first order. Cross linking between polymers through hydrogen bond formation occur as in the case of poly(methacrylic acid) and poly(ethylene glycol). The hydrogen bond formation takes place between the oxygen of poly(ethylene glycol) and carboxylic acid group of poly(methacrylic acid) Carriers consisting of networks of poly(methacrylic acid-g- ethylene glycol) showed pH dependent swelling due to the reversible formation of interpolymer complex, stabilized by hydrogen bonding between the etheric groups of the grafted poly(ethylene glycol), and t carboxylic acid protons of the poly(methacrylic acid).

Physically cross linked hydrogels

Most of the covalent cross linking agents are known to be toxic even in small traces method to overcome this to prepare hydrogels by reversible ionic cross linking. Chitosan, a polycationic polymer can react with positively charged components, either ions or molecules, forming a network through ionic bridges between the polymeric chains Among anionic molecules, phosphate bearing groups, particularly sodium tripolyphosphate is widely studied Ionic cross linking is a simple and mild procedure. In contrast to covalent cross linking, no auxiliary molecules such as catalysts are required. Chitosan is also known to form polyelectrolyte complex with poly (acrylic acid). The polyelectrolyte complex undergoes slow erosion, which gives a more biodegradable material than covalently cross linked hydrogels.

Mechanism of network formation: Gelation refers to the linking of macromolecular chains together which initially leads to progressively larger branched yet soluble polymers depending on the structure and conformation of the starting material. The mixture of such polydisperse soluble branched polymer is called ‘sol’. Continuation of the linking process results in increasing the size of the branched polymer with decreasing solubility. This ‘infinite polymer’ is called the ‘gel’ or ‘network’ and is permeated with finite branched polymers. The transition from a system with finite branched polymer to infinite molecules is called ‘sol-gel transition’ (or ‘gelation’) and the critical point where gel first appears is called the ‘gel point’ (Rubinstein&Colby, 2003). Different types of gelation mechanism are summarized in Figure 1.

Structure and properties of starch

Starch is mainly composed of two homopolymers of D-glucose; amylase, a mostly linear α- D(1, 4’)-glucan and branched amylopectin, having the same backbone structure as amylose but with many α-1, 6’-linked branch points (Figure 1). There are a lot of hydroxyl groups on starch chains, two secondary hydroxyl groups at C-2 and C-3 of each glucose residue, as well as one primary hydroxyl group at C-6 when it is not linked. Evidently, starch is hydrophilic. The available hydroxyl groups on the starch chains potentially exhibit reactivity specific for alcohols. In other words, they can be oxidized and reduced, and may participate in the formation of hydrogen bonds, ethers and esters. Starch has different proportions of amylose and amylopectin ranging from about 10–20% amylase and 80–90% amylopectin depending on the source. Amylose is soluble in water and forms a helical structure. Starch occurs naturally as discrete granules since the short branched amylopectin chains are able to form helical structures which crystallize. Starch granules exhibit hydrophilic properties and strong inter-molecular association via hydrogen bonding formed by the hydroxyl groups on the granule surface.

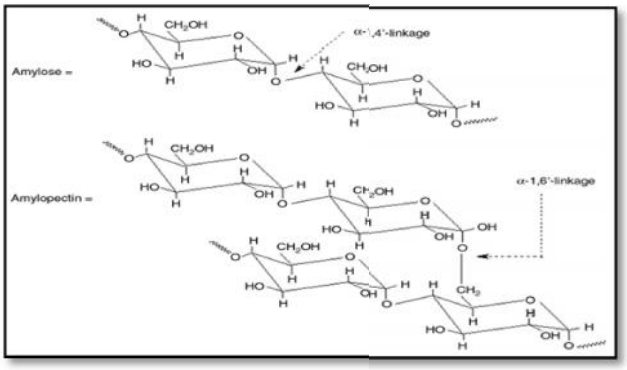

Figure 1

Dynamics of Swelling of Ionic Hydrogels

Water diffusion in glassy polymers often deviates from the predictions of Fick’s law, leading to anomalous or non-Fickian diffusional behavior. The deviation from Fickian behavior has been associated with the finite rate at which the polymer structure rearranges, to accommodate water molecules, and has been observed for many hydrophilic polymer systems. Depending upon the dynamics of polymer swelling and the relative mobilities of drug and water, Fickian or non-Fickian drug transport may be observed. The relative importance of water diffusion and polymer relaxation can be described by the Deborah number (De) defined as the ratio of a characteristic relaxation time (T) to a characteristic diffusion time (θ).

$$De=\tau/\theta,\ \theta=L / D$$

Where, L is the characteristic length of the controlled release device, Dis the water diffusion coefficient.

When De<<1, relaxation is much faster than diffusion, and Fickian transport is observed when De, 1 relaxation an diffusion are coupled leading to a complex transport behavior known as anomalous or non fickian transport. In fickian diffusion, the rate of water absorption shows a linear increase as a function of the square root of time. Fickian diffusion is observed when the time scale of the macromolecular relaxation is either effectively infinite or zero, compared to the time required to establish a concentration profile in the polymer sample. In non-Fickian or anomalous transport, both diffusion as well as macromolecular relaxation time scales is similar, and both control the overall rate of penetrant absorption. Case II transport is the limit, when relaxation predominates. Zero-order, time independent Case II kinetics are characterized by a linear mass uptake with time.

Advantages of Hydrogels

Hydrogels being three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids may offer several advantages they are,

- Sustained and prolonged action in comparison to conventional drug delivery systems
- Decreased dose of administration.
- Decreased side-effects.
- Improved drug utilization.
- Improved patient compliance.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy. Drug adapts to suit circadian rhythms of body functions or diseases.

Drug and polymer profile

Desvenlafaxine succinate

It is an anti depressant drug belonging to SNRI neither (Serotonin nor epinephrine Reuptake Inhibitor) category and majorly used in major depressive disorder.

Profile: Molecular formula: $C_{16}H_{25}NO_2$, Molecular weight: 263.38.

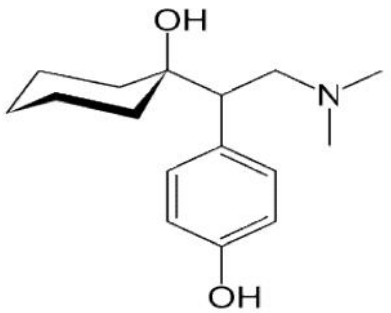

Figure 2

IUPAC name:

4-[2-dimethylamino-1-(1-hydroxycyclohexyl) ethyl] phenol

Physical properties: It occurs as white colour fine powder.

Melting point: 128^0C, Partition coefficient: 0.21, Ionization constant pK_a: 8.34 (dimethyl amino), 10.11 (phenolic group).

Biopharmaceutical Considerations

Bioavailability: 80%, Protein binding: 30%, Metabolism: CYP3A4, Half life: 11 hours,

Excretion: 45% unchanged in urine

Therapeutic Considerations: Route of administration: oral, Pregnancy category: C, Mechanism of action: SNRI,

Usage: depressive disorder, Dosage: 50-100 mg per day Drug interactions: Aspirin, Warfarin, ketoconazole, Desipramine Midazolam, Side effects: headache, dizziness, insomnia, fatigue, hyper hydrosis .

Polymer Profile

Starch

Non proprietary names: maize starch, potato starch, potato starch, corn starch

Synonyms: amido, amidon, amylum

Empirical formula: $(C_6H_{10}O_5)_n$

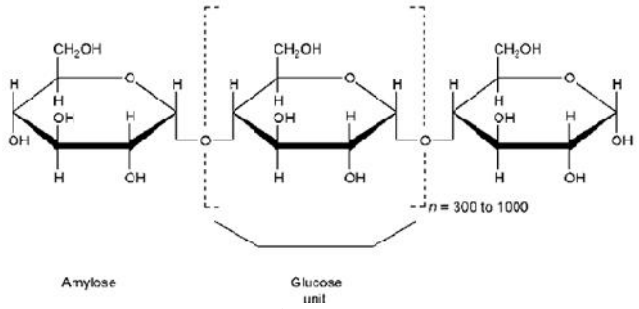

Figure 3

Functional category: glidant, tablet and capsule diluent, tablet disintegrant

Applications in pharmaceutical formulation or technology: starch is used as an excipient primarily an overall solid dosage forms formulations where it is utilized as it is a binder or diluents or disintegrant.

Description: starch occurs as an odorless and tasteless, fine white colored powder comprising very small spherical or ovoid granules

Typical Properties

Acidity or alkalinity: pH = 5.5 to 6.5, Density: 0.462 g/cm^3 for corn starch, Moisture content: all starches are hygroscopic and rapidly absorb atmospheric moisture, Particle size distribution: corn starch 2-32 mm, Solubility: practically insoluble in cold ethanol and in cold water, Swelling temperature: 658^0C corn starch, Stability and storage conditions: protected from high humidity, air tight container in a cool dry place, Safety:generally recognized as Safe ,Related substances: amylo pectin, A amylase, malto dextrin, starch, sterilizable maize.

2. Materials and Methods

The starch hydrogels were prepared by using corn starch as it possesses good amylase content. All the chemicals used were of analytical grade. The drug Desvenlafaxine succinate was procured as a gift sample from Matrix laboratories. Other ingredients procured were of analytical grade.

Corn starch (CS),

Ethanol,

Glutaraldehyde (GA),

Polyvinyl alcohol 10% (w/v) (PVA) mol. wt. 125000,
Hydrochloric acid 35%,
Double distilled water,
GA reagent was prepared by mixing 0.5ml of GA in a solution mixture of 10ml ethanol and 0.05ml Hydrochloric acid.

Method Development

Determination of absorption maxima in 0.9% Nacl

The primary stock solution of Desvenlafaxine was prepared by accurately weighing 100 mg of Desvenlafaxine and made upto 100 ml with 0.9% NaCl. Then the solution were taken and diluted to produce required concentrations with 0.9 Nacl. The aliquots were scanned in Double beam UV Visible Spectrophotometer (Systronics 2202) to identify lambda max and standard plot constricted using 0.9 % NaCl as blank.

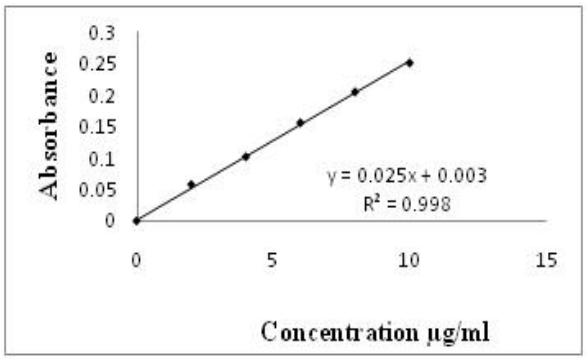

Figure 3: Calibration plot of Desvenlafaxine Succinate

Table 1: Optical characteristics of Desvenlafaxine Succinate in 0.9% NaCl

Parameters	Value
Absorption maxima	224 nm
Beers law range	2-10 µg/ml
Regression equation	y = 0.025x + 0.003
Correlation coefficient (R^2)	0.998

Formulation and Evaluation

Preparation of starch hydrogel

Fifty ml of 10% (w/v) PVA solution was taken in a beaker. To the PVA solution, 50ml of 5% (w/v) starch dispersion in water prepared by heating at 100^0C, was added with constant stirring to get a homogeneous mixture. To this mixture GA reagent (10.55ml) was added with constant stirring. Care was taken to eliminate entrapment of air bubbles during mixing and the mixture was used to obtain a membrane by the conventional solution casting method. The membrane was dried at room temperature. The membrane so obtained was transparent in nature. The membrane was washed thoroughly with distilled water to wash off hydrochloric acid and GA, if any. Then the membrane was dried at room temperature.

Table 2: Formula for preparation of starch hydrogels

Poly vinyl alcohol 10% (w/v)	50ml
Corn starch 5% (w/v)	50ml
Glutaraldehyde reagent	10.55ml

Weigh accurately 1gm of Desvenlafoxacine succinate drug dissolve in 0.9% Nacl. After that dried membrane cut into 6 pieces. The pieces was immerised directely in above solution at 72 hrs and the swollen piecies was dried at 37◦ C to a constant weight

Evaluation of Hydrogel

Swelling behavior

The membrane was immersed directly in 0.9% Nacl (prepared as per Indian Pharmacopoeia-1996) at room temperature for 72 hrs, and the swollen product was dried at 37º C to a constant weight. The equilibrium percentage of swelling (% swelling) of the product was calculated by using the following formula

$$\% \text{ Swelling} = (Wh-Wd)/Wd \times 100$$

Where, Wh is the weight of the product after hydration for 72 hrs while Wd is the weight of the dried product. The result was shown in table

Dissolution characteristics

Drug release from the hydrogel was studied using 8 station dissolution apparatus (Lab India DS8000) employing paddle stirrer at 50 RPM and at 37 ± 2^0C. The hydrogel after drug loading was dried and cut into suitable piece and it was put into dissolution bowl. The dissolution medium employed was 0.9%NaCl (900 ml). The drug release was measured by using UV Visible Spectrophotometer (Systronics 2202) from the developed method. The result was shown in the following table and the release kinetics were shown in figure

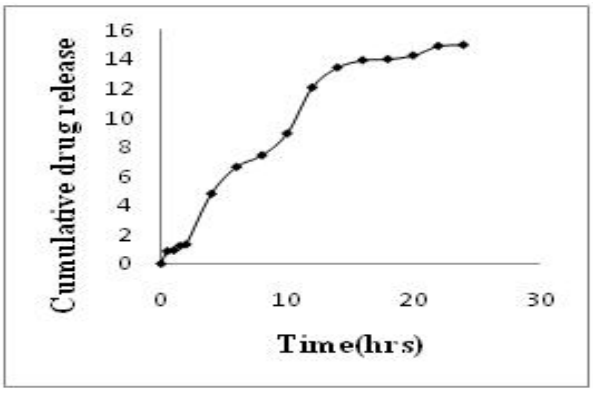

Figure 4: Release profile of various formulations

3. Results and discussions

Recently Desvenlafaxine is a serotonin nor adrenaline reuptake inhibitor and it is majorly used in obsessive depression disorder. For successful treatment of depression it is essential to maintain constant plasma drug concentration which can be achieved by giving the drug in controlled release dosage form which can improve the patient compliance. So, Desvenlafaxine is a suitable candidate to design controlled release dosage form. In present investigation the starch hydrogels were prepared by using corn starch as a polymer, Glutaraldehyde reagent as cross linking agent and poly vinyl alcohol as stabilizing agent. The hydrogels are novel promising controlled released dosage form which is gaining importance because of ease of manufacturing and diversified applications. The present trend of pharmaceutical research lies in the usage of

biodegradable polymer because of its availability and low toxicity. In the present study we have selected corn starch as biodegradable polymer which can be easily cross linked with Glutarldehyde and forms a gelly like consistency which is stabilized by polyvinyl alcohol.

The formed hydrogel was transfer into Petri plate and dried at room temperature for 48 hrs. After drying the swelling studies were performed by soaking the patch for 72 hrs and the average swelling of 160 % was found indicating good swelling property. After drying the patch of hydrogel was weighed and it is cut into pieces of 1cm×1cm and soaked is saturated drug solution for 72hrs and dried at room temperature for 48 hrs and proceeded for dissolution studies using 0.9% NaCl as dissolution medium. Drug release from the hydrogel patch was studied by using 8 station dissolution rate test apparatus (LAB INDIA DS8000) employing a paddle stirrer at 50rpm and at 37±1^{o}c .0.9%Nacl (900ml) as dissolution medium samples of 5 ml each were withdrawn at different time intervals over a period of 24 hrs and it is replaced with equal amount of fresh dissolution medium. Samples were diluted and analysed at 224 nm for Desvenlafaxine using systronics UV Visible double beam Spectrophotometer 2202. The results of the dissolution studies showed that 14.96mg of Desvenlafaxine was released at the end of 24 hrs. From the dissolution data kinetics has been calculated. The peppas equation showed the 'n' value of 0.94 indicating the drug release from hydrogels follows non fickian diffusion and R^2 of 0.950. The release mechanism was nearly following zero order release.

4. Conclusion

Corn starch is abundantly available in nature with the help of it we can prepare controlled release dosage form starch hydrogen is the current area of research for developing various dosage forms starch hydro gels are prepared easily with the normally available ingredients the major advantage of hydrogen is the control release behavior up to 24 hrs the present starch hydrogen was able up to 24 hrs.The drug release studies were performed and the dissolution studies was fit into various kinetic and the drug release mechanism was found to be non fickian diffusion type.

Table 1: Swelling characteristics of Hydrogels

S. No	Wh	Wd	% of swelling	Average % swelling
1	0.275	0.11	150	160
2	0.312	0.12	160	
3	0.336	0.12	180	
4	0.325	0.13	150	
5	0.260	0.10	160	
6	0.028	0.14	160	

Table 2: Release profile of Desvenlafaxine Succinate from Hydrogels

Time (hrs)	Cumulative drug release (mg)						
	H1	H2	H3	H4	H5	H6	AVG
0	0	0	0	0	0	0	0
0.5	0.863	0.864	0.865	0.862	0.864	0.866	0.864
1	0.930	0.920	0.925	0.923	0.924	0.920	0.923
2	1.228	1.219	1.225	1.236	1.214	1.224	1.224
4	1.331	1.324	1.329	1.325	1.326	1.321	1.326
6	4.788	4.789	4.789	4.787	4.788	4.787	4.788
8	6.624	6.625	6.622	6.623	6.627	6.628	6.624
10	7.420	7.421	7.420	7.422	7.425	7.425	7.420
12	8.908	8.907	8.905	8.906	8.907	8.906	8.906
14	12.02	12.09	12.080	12.06	12.08	12.04	12.06
16	13.90	13.92	13.92	13.94	13.92	13.96	13.92
18	13.99	13.99	13.96	13.98	13.97	13.98	13.99
20	14.24	14.25	14.24	14.24	14.26	14.24	14.24
22	14.89	14.89	14.86	14.88	14.88	14.87	14.89
24	14.96	14.95	14.93	14.99	14.95	14.99	14.96

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