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Evaluation of microwave assisted grafted sago starch as controlled release polymeric carrier

Akhilesh Vikram Singh [a,b,*], Lila Kanta Nath [b]

[a] Biomaterials Lab, Department of Materials Engineering, Indian Institute of Science, Bangalore 560012, Karnataka, India
[b] Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004, Assam, India

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ABSTRACT

In the present investigation an attempt has been made to develop a new co-polymeric material for controlled release tablet formulations. The acrylamide grafting was successfully performed on the backbone of sago starch. The modified starch was tested for acute toxicity and drug–excipient compatibility study. The grafted material was used in making of controlled release tablets of lamivudine. The formulations were evaluated for physical characteristics such as hardness, friability, %drug content and weight variations. The *in vitro* release study showed that the optimized formulation exhibited highest correlation (R) value in case of Higuchi model and the release mechanism of the optimized formulation predominantly exhibited combination of diffusion and erosion process. There was a significant difference in the pharmacokinetic parameters (T_{max}, C_{max}, AUC, V_d, $T_{1/2}$ and MDT) of the optimized formulation as compared to the marketed conventional tablet Lamivir® was observed. The pharmacokinetics parameters were showed controlled pattern and better bioavailability. The optimized formulation exhibited good stability and release profile at the accelerated stability conditions.

1. Introduction

During the past few decades research in the field of formulation development has been focused on the search for systems that delay the release of drug after their administration. A hydrophilic matrix is a homogeneous dispersion of drug molecules with the excipients like hydrophilic polymer (cellulose derivatives, sodium alginate, xanthane gum, polyethylene oxide or carbopol) that swells upon contact with water. Reservoir and matrix type tablets are the most commonly used orally administrated sustained release preparations [1]. Especially matrix tablets, which are produced by direct compression using either hydrophilic polymer such as natural gums, HPMC, CMC, carbopol or hydrophobic polymer like ethyl cellulose and amylodextrin, are relatively easy to manufacture [2]. For many reasons, oral drug delivery continues to be the preferred route of administration of drug substances. During the last two decades, polymers which swell in aqueous media has been used for preparation of oral sustained release dosage forms. Lamivudine (LAM) is the first nucleoside analog approved to treat chronic HBV infection and AIDS. Conventional oral formulations of LAM are administered two times a day 150 mg at a time because of its moderate half-life ($T_{1/2}$ = 5–7 h). Treatment of AIDS using conventional formulations of LAM is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost [3]. In our laboratory we synthesized various chemically modified derivatives of sago and moth bean starch for controlled release applications [4–6]. The aim of the present study was to establish the grafted sago starch (GSS) as controlled release excipient in the controlled release tablets formulation. Recently we have successfully synthesized acrylamide grafted moth bean starch as controlled release polymer [7]. The aim of the present study was to evaluate the chemically modified (grafted) sago starch as hydrophilic inert matrix former in the formulation of controlled release tablets of LAM by direct compression technique. The formulated tablets were evaluated for various physical characteristics, *in vitro* dissolution study and *in vivo* pharmacokinetic study in rabbit model.

2. Materials and methods

2.1. Materials

Lamivudine (LAM) was kindly gifted by Ranbaxy Limited, Paonta Sahib, Himachal Pradesh, India. Sago starch was procured from the local market of Chennai, Tamil Nadu, India. Spray dried lactose (SDL) was kindly donated by DMV Fonterra excipients, The Netherland. Polyvinyl pyrrolidine K-30 (PVP K-30), magnesium

* Corresponding author. Current address: Biomaterials Lab, Department of Materials Engineering, Indian Institute of Science, Bangalore 560012, Karnataka, India. Tel.: +91 9880342352.
E-mail address: akhileshvikram@gmail.com (A.V. Singh).

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stearate and talc were purchased from Loba Chemie Limited, Mumbai, India. All other chemicals used were of analytical grade and purchased from SD Fine chemical limited, Mumbai, India.

Digital weighing balance (Sartorius, Germany), Rotary ten station tablet punching machine (Shakti Engineering Limited, Ahmedabad, India). UV-Visible Spectrophotometer (UV-1700, Shimadzu, Japan), HPLC (Waters®, USA), Eight basket digital *in vitro* USP dissolution apparatus (Electrolab, Mumbai, India), Monsano hardness tester and Roche friabilator (Campbell Electronics, Mumbai, India), Laboratory scale stability chamber (Model TH-90 S/G, Thermolab, Mumbai, India).

2.2. Microwave assisted acrylamide grafting on sago starch

Sago starch was pregelatinized by heating the aqueous starch dispersion at 75 °C. The pregelatinized sago starch was grinded and sieved through 100 mesh screen. Pregelatinized sago starch (1.0 g) was dispersed in 50 mL of double distilled water. Various amounts (2.5–10.0 g) of acrylamide (AMD) were dissolved in 15 mL of water and were added to the starch dispersion. They were mixed well using stirrer and was transferred to a conical flask (250 mL) and CAN (0.25 g) was added. The flask was subsequently placed on the turntable of a microwave oven (CE1111L, Samsung Electronics, India). The flask was irradiated at various microwave power (250–600 W). After formation of a gel mass the flask was placed in ice-cold water. The flask was kept undistributed for 12 h to complete the grafting reaction. After 12 h, 0.5 mL saturated solution of Hydroxyquinone was added to terminate the grafting reaction. The gel mass was poured in excess of acetone. The grafted copolymer was purified by solvent extraction method using a mixture of formamide and acetic acid (1:1). The resulting precipitate of graft copolymer was collected and was dried in hot air oven. The grafted material was grinded until a homogenous powder was obtained [8,9].

2.3. Acute toxicity study of grafted copolymer

Healthy male and female Swiss Albino mice (8 weeks) were used for the acute oral toxicity study. The temperature in the animal house was maintained at 25 ± 2 °C with a relative humidity of 30–70% and illumination cycle set to 12 h light and 12 h dark. All the mice of both the sexes were fasted overnight before experimentation and were allowed to take food 1 h after the experiment. Grafted starch was administered orally at a dose of 2000 mg/kg b.w. in distilled water. The animals were observed for any mortality and morbidity (convulsions, tremors, grip strength and pupil dilatation) at an interval of 12 h for 14 days. This study was approved by the Animal Ethical Committee of Gayatri College of pharmacy (Regn. No.1339/ac/10/cpcsea).

2.4. Preformulation study

2.4.1. Drug–excipient compatibility study by DSC

A differential scanning calorimetry (JADE DSC, Perkin Elmer, USA) was used to study the thermal analysis of drug–excipient compatibility. Firstly, binary mixtures of lamivudine and excipients (in 1:1 mass/mass ratio) were prepared by using physical mixture technique. The drug–excipient mixture was scanned in the temperature range of 50–220 °C under an atmosphere of nitrogen. The heating rate was 20 °C/min and the obtained thermograms were observed for any type of interaction.

2.4.2. Drug–excipient compatibility study by FT-IR spectroscopy

FT-IR spectra were recorded on a Bruker spectrophotometer (Model – 220, Germany) using KBr discs in the range of 4000–450 cm^{-1}. FT-IR analysis has been performed using samples of lamivudine with various excipients and grafted starch at 1:1 mass/mass ratio.

Table 1
Composition of lamivudine controlled release tablets using GSS.

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Lamivudine	100	100	100	100	100	100
Grafted sago starch (GSS)	25	50	75	100	125	150
PVP K-30	15	15	15	15	15	15
Lactose	q.s.*	q.s.*	q.s.*	q.s.*	q.s.*	q.s.*
Magnesium stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total weight	300	300	300	300	300	300

q.s.*, quantity sufficient.

2.4.3. Isothermal stress testing (IST) analysis

In isothermal stress testing [10,11] samples of drug and different excipients were weighed directly in 5 mL glass vials ($n = 3$). After mixing on a cyclomixer for 3 min, 10% (w/w) water was added in each of the vial. The glass vials, after Teflon sealing, were stored at 50 °C in hot air oven. Drug–excipient blends without adding water and stored in refrigerator served as controls. The drug–excipient blends were periodically examined for any change in physical appearance. Samples were quantitatively analyzed using UV–vis spectrophotometer (Pharmaspec 1700, Shimadzu, Japan) after 4 weeks of storage at above conditions.

2.5. Formulation of tablets

The lamivudine controlled release tablets were formulated by direct compression technique. The selected amount of drug and excipients for each batch is tabulated in Table 1. Lamivudine, grafted sago starch (GSS), spray dried lactose and PVP K-30 were dispensed accurately. Each ingredient was shifted through # 80 sieves, transferred in to a polyethylene bag and mixed for 20 min. The lubricated dry powder was compressed into tablets at 8 kg/cm^2 pressure by using 10 mm standard flat punch set in 10 station rotary tablet punching machine. The tablets were double wrapped in polyethylene bag till further study.

2.6. Evaluation of tablet

The tablets from each batch were picked randomly in order to evaluate the weight variation, the hardness, %drug content and the friability [12]. The hardness and friability of the tablet were measured using Monsanto hardness tester and Roche friabilator respectively.

2.7. In vitro dissolution rate study

In vitro dissolution rate study of the formulations ($n = 6$) was carried out in USP Type-II dissolution rate test apparatus. Dissolution rate study was performed in simulated gastric fluid (0.1 M HCl) and in simulated intestinal fluid (PBS pH 6.8) for 2h and for successive 10 h respectively. The each dissolution medium (900 mL) was maintained at 37 ± 0.5 °C throughout the study. The samples (5 mL) were withdrawn at predetermined time (1, 2, 3, 4, 6, 10, and 12 h) and replaced with an equivalent volume of fresh medium. The samples were filtered through membrane filter (0.45 μm) and analyzed by UV–vis spectrophotometer at 270 nm λ_{max} [13]. The cumulative percent drug release was plotted against time to determine the release profile.