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ORIGINAL ARTICLE

Mucoadhesive nanoparticles from tamarind seed polysaccharides for sustained delivery of anticancer drug irinotecan

Pranjal Saikia, Bhanu P. Sahu, S. K. Dash

Department of Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Science, Azara, Guwahati, Assam, India

The present study is aimed at development and optimization of mucoadhesive nanoparticles (NPs) from natural mucoadhesive polysaccharides extracted from Tamarind seeds *(Tamarindus indica)* for the sustained delivery of anticancer drug irinotecan. The drug loaded NPs were prepared by ion gelation method with the isolated polysaccharide by homogenization followed by lyophilization. The polysaccharides were cross-linked with sodium alginate in different ratios. The formulations were optimized using two level factorial design (Design Expert - 8.0.7.1) using the polysaccharide to alginate ratio, homogenization time and homogenization speed as independent variables and particle size (PS), drug entrapment efficiency and cumulative drug release as the dependent variables. The NPs were characterized in terms of PS, entrapment efficiency, drug loading (DL), *in vitro* drug release and cell viability studies in mice. Stable NPs were obtained with average PS of 405 ± 25.2 nm. The preparations were homogenous showing polydispersity index of 0.497 ± 0.02. The formulation showed up to 95.36 ± 3.1% (w/w) yield showing DL of 1.0 ± 0.2% (w/w). The entrapment efficiency was found to be 46.56 ± 1.5% (w/w). *In vitro* drug release showed initial burst release followed by controlled release pattern showing up to 60% release in 12 h. The average cell viability was found to be 80% in case of the control group, which was reduced to 36% for NPs treated groups respectively. The Fourier transform infrared studies showed no incompatibility in the formulated NPs. It may be concluded from the study that tamarind seed polysaccharides may be suitable for formulation of mucoadhesive NPs for better efficacy and sustained delivery of anticancer drug irinotecan with reduced toxicity.

Key words: *Homogenization, irinotecan, mucoadhesive, nanoparticles, tamarind*

INTRODUCTION

Nanoparticulate drug delivery system has emerged to be an important area in the field of delivery of anticancer drugs. Nanoparticles made from natural hydrophilic polymers have been proved efficient in terms of better drug-loading capacity, biocompatibility and possibly less opsonization by the reticuloendothelial system through an aqueous steric barrier. Mucoadhesive NPs made up of hydrophilic polysaccharides may also sustain the release of drug and hence improved bioavailability.

Irinotecan is an antineoplastic enzyme inhibitor primarily used in the treatment of colorectal cancer. It is a hydrophilic analogs or prodrugs of the camptothecin that inhibits the action of topoisomerase I. Irinotecan prevents religation of the deoxyribonucleic acid (DNA) strand by binding to topoisomerase I-DNA complex and causes double-strand DNA breakage and cell death. It is available as irinotecan hydrochloric acid (HCl) (40 mg/2 ml injection), Camptosar (20 mg/ml vial), irinotecan HCl (40 mg/2 ml vial) for i.v. administration. IV administration of these causes severe side-effects due to the rapid drug distribution.[1,2] The active compound of irinotecan, is a hydrophobic analog of camptothecin alkaloid that has 1000-fold higher activity *in vitro* than irinotecan, but its extreme hydrophobicity has prevented its clinical use.[3] Therefore, sustained release of the drug has been proposed in to minimize the adverse reaction of drug in the whole body.[4-6]

Address for correspondence:
Dr. Bhanu P Sahu,
Department of Pharmaceutics,
Girijananda Chowdhury Institute of Pharmaceutical Science,
Azara, Guwahati - 781 017, Assam, India.
E-mail: pratapsuman2004@yahoo.co.in

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Tamarind is a common tree of India and Southeast Asia, which belongs to dicotyledonous family *Leguminosae*. A mucoadhesive polymer extract obtained from the seed kernel of *Tamarindus indica*, possesses high viscosity, broad pH tolerance, non-carcinogenicity, mucoadhesive property and biocompatibility.[7,8] Tamarind seed polysaccharide (TSP) isolated from tamarind kernel powder shows sustained release behavior for both water-soluble (acetaminophen, caffeine, theophylline and salicylic acid) and water insoluble (indomethacin) drugs.[9] In addition to this TSP have shown high drug holding capacity[10] and high thermal stability.[11] This has led to its application as excipient in hydrophilic drug delivery system. A number of mucoadhesive formulations have been developed using TSP for drugs such as gentamycin, ofloxacin,[12] paclitaxel,[13] ketotifen fumarate[14] with improved efficacy.

The present study was therefore aimed at preparing mucoadhesive NPs of irinotecan using TSP by ion gelation technique to attain sustained delivery with reduced adverse effects.

MATERIALS AND METHODS

The tamarind seeds were collected locally. All the chemicals used during the project are of analytical grade. Irinotecan hydrochloric acid (HCl) was purchased from Yarrow Chem. Products, Mumbai, India. Acetone, HCl, sodium hydroxide, sodium dihydrogen phosphate, potassium dihydrogen phosphate were purchased from Merck Specialties Pvt. Ltd., Mumbai. Ethanol was purchased from ThangshuYngyuan Chemical, China.

Preparation of NPs

NPs were prepared by ion gelation method followed by homogenization. Sodium alginate solution (5%) was first mixed with TSP solutions (5%) in different ratios to form an alginate: TSP mixture to make the ion gelation proper. Polysaccharide micro beads were prepared using micro syringe by adding alginate: TSP mixture containing the drug (0.2%) dropwise in 30 ml of 5% calcium chloride solution and allowed to stir for 30 min. The obtained microbeads were recovered and hardened in acetone. The hardened microbeads were then dispersed in acetone and subjected to high speed homogenization (10,000-12,000 rpm) for 15-30 min. The prepared NPs were lyophilized and stored in well closed moisture resistant container. The process is found to be good in 2:1 TSP to sodium alginate ratio in w/w. It can be maximize up to 4:1 ratio but after lyophilization it was found to be very sticky in nature.

Characterization of NPs

Drug loading and drug entrapment efficiency

A known quantity of drug loaded NPs (20 mg) from each batch was dispersed in 20 ml phosphate buffer saline (PBS) solution and sonicated for ½ h. The solution was then centrifuged at 10,000 rpm for 15 min and the absorbance was determined using ultra violet (UV) spectrophotometer at 254 nm.[15,16] The DL was obtained by the Equation 1 and the DEE was obtained using Equation 2.

$$\%\ DL = \text{Amount of drug in NPs/amount of drug-loaded NPs} \times 100 \quad (1)$$

$$\%\ DEE = \text{Amount of drug in NPs/total amount of drug} \times 100 \quad (2)$$

Particle size determination

The PS analysis of the lyophilized nanoaparticles (average apparent diameter, D) and polydispersity index (PDI) were determined by dynamic light scattering using Zetasizer (Malvern Nano S90). Determinations were carried out at 25°C at a fixed angle of 90°. NPs were dispersed in distilled water solution before measurement. Results are shown in Table 1 and Figure 1a-c.

Optimization of formulation using factorial design

A 2^3 full factorial design was selected for the formulation and optimization of the NP formulations. The polysaccharide to alginate ratio (X_1), homogenization time (X_2) and homogenization speed (X_3) were selected as the factors and were accordingly varied and the factor levels were suitably coded. The suggested formulations given by the Design-Expert software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN) were systematically prepared and characterized for PS (Y_1), DEE (Y_2) and cumulative drug release (CDR) (Y_3) as the dependent variables. In this design, three factors are evaluated, each at three levels and experimental trials were performed for all possible combinations. All other formulation variables and processing variables were kept invariant throughout the study. The results are shown in Table 1.

The effect of the independent variables X_1, X_2 and X_3 on the response (Y) was observed. The regression equation for the response was calculated using the following Equation 3.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_1b_2X_1X_2 + b_2b_3X_2 \times_3 + b_3b_1X_3X_1 \quad (3)$$

Where Y is dependent variable, b_0 is arithmetic mean response of 8 runs and b_i (b_1, b_2, b_3, b_1b_2, b_2b_3, b_3b_1) is estimated for corresponding factor X_i (X_1, X_2, $X_3X_1X_2$, X_2X_3, X_3X_1) which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in response when two factors are simultaneously changed.[17]

Optimization, data analysis and desirability function

The NP formulations were optimized by employing Design-Expert software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN) using various response surface methodology. Polynomial models including quadratic equations were generated for all the response variables. In addition, 3D graphs were constructed using the output files

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Table 1: Different formulation batches and their particle size, drug entrapment efficiency and drug release

Batch	TSP to alginate ratio (w/w)	Speed (rpm)	Time (min)	Particle size (nm)	Drug entrapment efficiency (%)	Cumulative drug release (%)
A	2:1	10,000	30	499.9	40.28	22.25
B	1:1	12,000	15	619.4	34.33	38.79
C	2;1	12,000	15	701.9	27.41	32.21
D	1:1	10,000	15	657.9	38.26	30.88
E	2:1	10,000	15	546.9	38.55	36.04
F	1:1	10,000	30	454.6	42.09	40.67
G	1:1	12,000	30	659.4	38.44	37.87
H	2:1	12,000	30	405.5	46.56	64.42

TSP: Tamarind seed polysaccharides

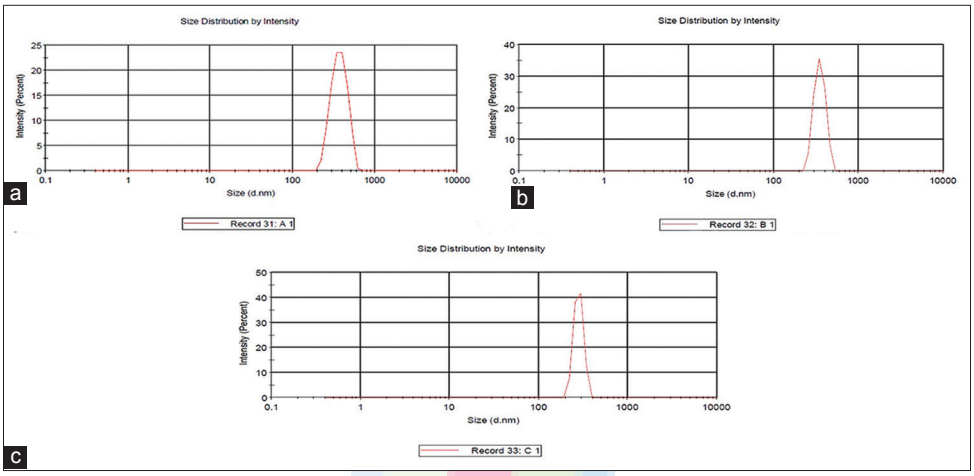

Figure 1: (a) Particle size distributions of some formulations (Batch A). (b) Particle size distributions of some formulations (Batch B). (c) Particle size distributions of some formulations (Batch C)

generated by the Design-Expert software. The significance of these factors on the variable parameters was assessed by analysis of variance (ANOVA, 2-way).The results of ANOVA studies are shown in Table 2.

After fitting of the mathematical model, the desirability function was used for the optimization. During optimization of the formulations, the responses were combined to find a product having the desired characteristics. The desirability function combines all the responses into one variable to predict the optimum levels for the independent variables. A desirability value of 0 represents an unacceptable value for the responses and a value of 1 represents the most desired value for the responses. Finally, the proposed optimized formulations as selected by the design were prepared and the parameters were observed and compared to the expected values as given by the design.

Fourier transforms infrared spectroscopy

Drug excipients interactions were studied by FTIR spectroscopy. The FTIR spectra were recorded for pure drug Irinotecan, polysaccharide and the lyophilized NPs. Samples were prepared in KBr discs (2 mg drug in 8 mg KBr) with a hydrostatic press at a force of 8 t/cm for 2 min. The scanning range was 450-4,000/cm and the resolution was 2 cm^{1}.

In vitro drug release study

Even though Irinotecan is an important anticancer drug, intravenous administration of Irinotecan causes severe side effects due to the rapid drug distribution into the whole body. Therefore, sustained release profile has been proposed in nano-sized drug delivery system that could minimize the adverse reaction of drug in the whole body. To evaluate the drug release profile of drug loaded NPs, they were immersed at 37°C in PBS (pH 7.4) and time-dependent drug release profile was measured under physiological condition using dialysis bag technique. Briefly 100 mg of lyophilized NPs was dispersed in a 5 ml of distilled water. 1 ml of this dispersion was added in a dialysis bag immersed in in 30 ml of PBS maintained at 37°C and magnetically stirrered at 50 rpm. At selected time intervals, 2 ml samples were withdrawn up to 12 h and replaced with 2 ml of fresh PBS. The samples were then analyzed using UV spectrophotometer (Shimadzu) at 254 nm.[18]

In vivo efficacy and tolerability studies

Cell viability study was conducted in 18 Albino mice (20-25 g; 6/group) divided into three groups (A, B, C). These mice were inoculated with 1 × 10^{6} (50 µL) esophageal adenocarcinoma (EAC) cells subcutaneously on the peritoneum to develop tumors. Once the tumor was

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Table 2: Summary of ANOVA results for response surface full factorial design of PS, %DEE, and %CDR

Response	Model	Sum of squares	*F* value	Prob>*F*	Inference
PS	Full factorial	81326.99	475.58	0.0351	Significant
DEE	Full factorial	220.82	36.80	0.0401	Significant
CDR	Full factorial	1055.39	331.60	0.0420	Significant

ANOVA: Analysis of variance, DEE: Drug entrapment efficiency, SD: Standard deviation, CDR: Cumulative drug release, PS: Particle size

established a single dose (20 mg/kg) of pure drug irinotecan and drug loaded NPs formulation was administered through i.p route (200 µL) to group B and C respectively. Ascites formation was monitored daily. All animal studies were conducted in accordance with the CPCSEA or Institutional Animal Ethics Committee. Mice were housed under standard conditions with enrichment and provided food and water *ad libitum*. They were observed at least two times per day for morbidity, more if deemed necessary during the pre-treatment and treatment periods. The therapeutic effectiveness of a single i.p dose (20 mg/kg irinotecan) of NPs formulations was compared with that of single irinotecan (20 mg/kg) for the treatment of mice bearing subcutaneous EAC xenografts. Viable as well as non-viable cell counting was done with automated cell counter (INVITROGEN™) using the trypan blue exclusion method[19,20] to observe the *in vivo* efficacy of the treatments. The dose was selected from the maximum recommended therapeutic dose and LD_{50} of irinotecan in mice.

RESULTS AND DISCUSSIONS

Drug loading and drug entrapment efficiency

It has been observed from the literature that it is very difficult to load a water soluble drug in a considerable amount in aqueous media using ion gelation technique as most of the drugs come out from the hydrophilic polysaccharide matrix. However in the present study substantial amount of DL up to 1.0% ± 0.2% (w/w) was obtained. Moreover, a substantial amount of drug entrapment up to 46.56% ± 1.5% (w/w) was obtained in the NPs prepared by the ion gelation method using a mixture of Tamarind polysaccharide and sodium alginate.

PS and PDI

The lyophilized drug loaded NPs were found to be in the range 405.5 nm to 701.9 nm. After DL no significant variations were observed among the different batches. The PDI were found to be in the range 0.5-0.8 for the drug loaded NPs, which indicates the formation of homogenous NPs. Although no redispersing agent was added during the lyophilization of the NPs, the formulations were found to be readily redispersible. This may be due to the presence of tamarind polysaccharides, which are very good self redispersant.

Statistical experimental design

The formulations were optimized using two level factorial designs (Design Expert-8.0.7.1, Stat-Ease Inc., Minneapolis, MN). The polysaccharide to alginate ratio, homogenization time and homogenization speed were taken as factors and PS, %DEE and %CDR as used as dependent variables. From the preliminary studies, the TSP to sodium alginate ratio was selected in the range of 2:1 maximum and 1:1 minimum. The homogenization speed was fixed in the range 10,000-12,000 rpm because at very high speed the decrease in PS is accompanied with an increase in the surface charge, which may cause more aggregation after lyophilization. Homogenization time was found to be satisfactory in the range 15-30 min.

Influence of independent variables on PS

The effect on PS (Y_1) was observed to be significant by ANOVA and the polynomial equation was found as follows:

$$Y_1 = 568.19 + 33.84X_1 + 28.36X_2 - 63.34X_3 + 50.26X_1X_2 + 40.96X_1X_3 - 0.76X_2X_3 \quad (4)$$

(Where X_1-TSP ratio, X_2-homogenization speed, X_3-time duration of homogenization).

From the polynomial equation it was observed that the PS decreases with increasing TSP ratio in the mixture. Similarly increase in homogenization speed and time also results in reduction of PS. No significant interaction was however observed between speed and time. The response surface graph is shown in Figure 2a.

Influence of independent variables on DEE

The effect on entrapment efficiency (Y_2) was observed to be significant by ANOVA and the polynomial equation was found as follows:

$$Y_2 = 38.24 - 2.07X_1 - 1.56X_2 + 3.60X_3 - 1.69X_1X_2 - 0.41X_1X_3 + 2.21X_2X_3 \quad (5)$$

(Where X_1-TSP ratio, X_2-homogenization speed, X_3-time duration of homogenization).

The polynomial equation shows that the DEE increases when amount of TSP increases, whereas it decreases with an increase in speed and time. This may occur at high speed as because the drug particles escape the entire polysaccharide matrix at very high speed and if the process is carried out for the prolong period results in decreased drug entrapment. No significant interaction was observed in between TSP ratio and time. The response surface graph is shown in Figure 2b.

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Influence of independent variables on CDR

The effect on CDR (Y_2) was similarly observed to be significant by ANOVA and the polynomial equation was found as follows:

$$Y_3 = 37.48 - 5.95X_1 + 5.34X_2 + 3.36X_3 - 2.70X_1X_2 - 5.60X_1X_3 + 4.27X_1X_2 \quad (6)$$

(Where X_1-TSP ratio, X_2-homogenization speed, X_3-time duration of homogenization).

From the equation it is observed that CDR increases at high TSP ratio. Increase in homozenization time causes less drug entrapment and hence less amount drug release. No significant interaction was observed in between TSP and speed. The response surface graph is shown in Figure 2c.

Formulation optimization using the desirability function

The aim of pharmaceutical formulation optimization is generally to find the levels of the variable that affect the chosen responses and determine the levels of the variable from which a robust product with high quality characteristics may be produced. All the measured responses that may affect the quality of the product were taken into consideration during the optimization procedure. Upon "trading off" different response variables, the following criteria were adopted: PS ≤1000 nm and minimized, drug release ≥25% and maximized and DEE above 25% and maximized. The responses of factorial formulations suggested a TSP - alginate ratio of 2:1 at homozenization speed of 12,000 rpm for 30 min as the optimized formulation. The selected optimized formulation was prepared and the observed values were found to be quite comparable to the predicted values as shown in Table 3.

Comparative FTIR study of NPs formulation with polysaccharide and pure drug

The FTIR study was recorded for pure irinotecan, polysaccharide and the lyophilized NPs for any possible drug-excipient interactions. From the FTIR study it was observed that the major peaks of 3412.46, 2943.53, 2541.43, 1656.66 and 1455.19 of pure drug irinotecan were found to remain intact in the spectra of lyophilized NPs. Very less stretching or broadening of peaks of the drug was observed in formulation

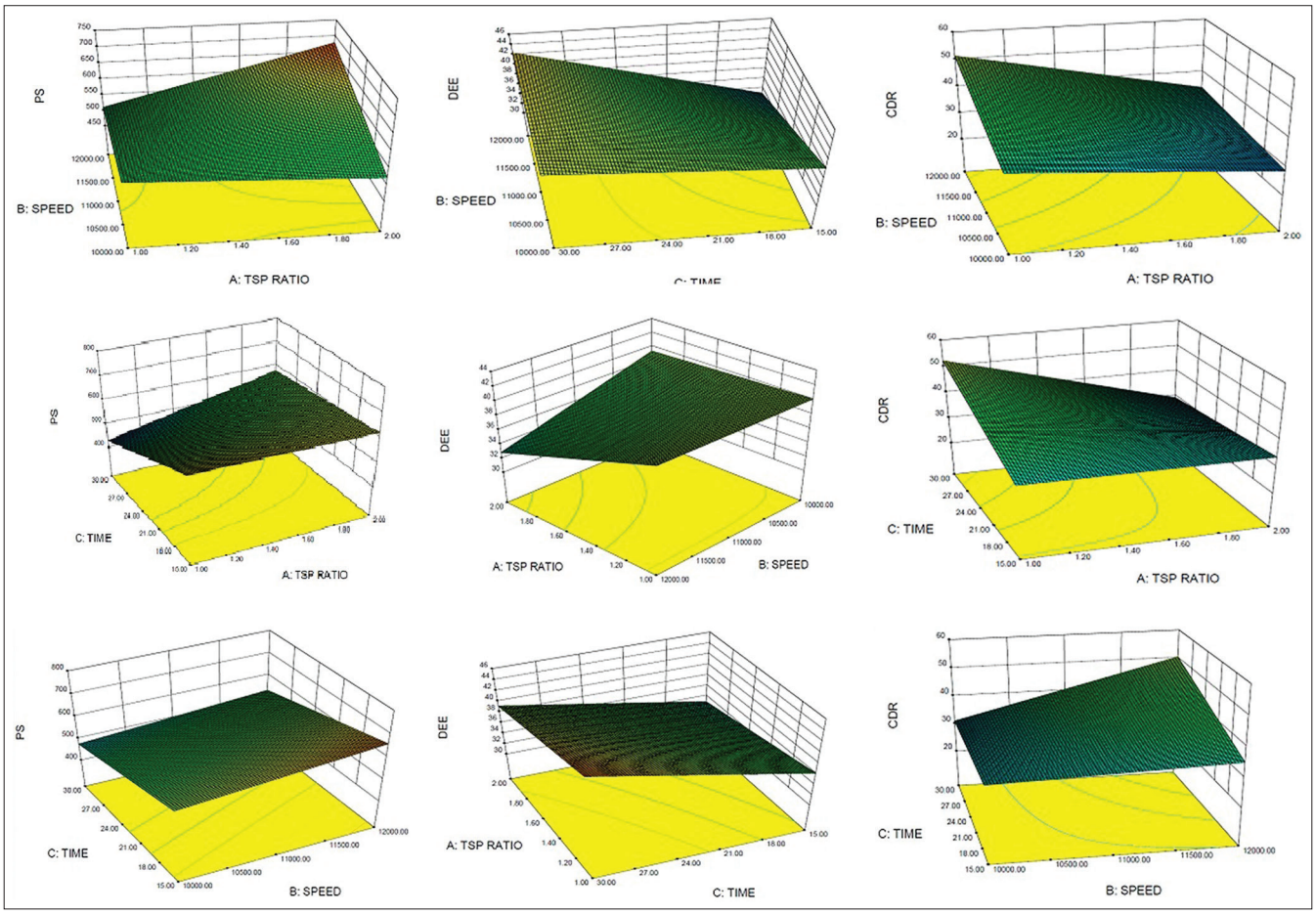

Figure 2: (a1) Response surface curves for particle size (effect of tamarind seed polysaccharide [TSP] ratio and speed). (b1) Response surface curves for drug entrapment efficiency (effect of speed and time). (c1) Response surface curves for cumulative drug release (effect of speed and TSP ratio). (a2) Response surface curves for particle size (effect of time and TSP ratio). (b2) Response surface curves for drug entrapment efficiency (DEE) (effect of TSP ratio and time). (c2) Response surface curves for cumulative drug release (effect of time and TSP ratio) (a3) Response surface curves for particle size (effect of time and speed). (b3) Response surface curves for DEE (effect of TSP ratio and speed). (c3) Response surface curves for cumulative drug release (effect of time and speed)

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form. This indicates the absence of any interaction between drug and the excipients. The results are shown in the Figure 3.

In vitro drug release study

The drug-loaded nano-formulations showed a biphasic sustained release pattern. An initial burst release was observed within 1 h followed by a sustained release up to 60% in 12 h indicating the potential of drug loaded NPs as a sustained drug delivery system. The initial release may be due to the release of drug adhered to the surface of the particles, which is followed by a controlled diffusion through polysaccharide matrix. The cross linked polymer matrix of tamarind polysaccharides and sodium alginate resulted in a sustained drug release for 12 h. The comparative drug release is shown in Figure 4. Most of the formulations showed a sustained drug release up to 40% ±4% in 12 h however formulation H (Optimized formulation) showed a maximum drug release of 64% in a sustained manner. This higher release may be attributed to the higher drug entrapment and reduced PS of the NPs.

In vivo efficacy and tolerability studies

For the antitumor efficacy study 3 groups (A, B, C) were selected as control, pure drug irinotecan treated and drug loaded NPs treated respectively. The study was conducted for 14 days. Animals were sacrificed and cell viability was determined using automated cell counter (INVITROGEN™). Cell sizes were detected in between the range 5-60 µm. From the study the average cell viability was found to be 80% in case of control group, which was reduced to 34% for NPs treated groups as shown in Figure 5a and b respectively. High mortality was observed in case of pure drug treated group than NPs treated group at the given dose. It may be due to high gastrointestinal toxicity of the drug on sudden exposure on i.p. administration. The controlled and sustained releases of drugs from the irinotecan NPs resulted in lesser morbidity compared with pure drug and hence were much safer than that of free drug. Further *in vivo* study is required for better interpretation of results.

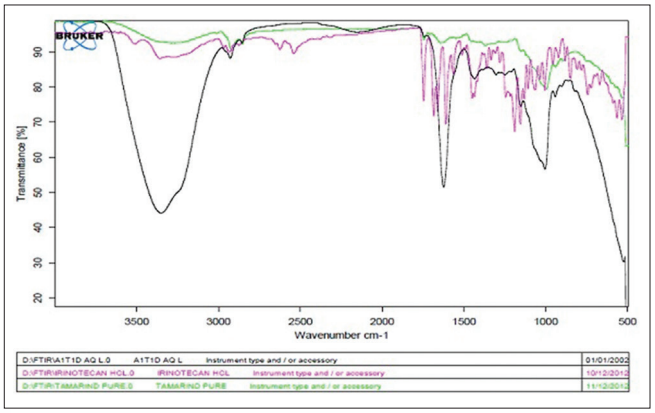

Figure 3: Comparative Fourier transforms infrared spectrum of NPs formulation with polysaccharide and pure drug

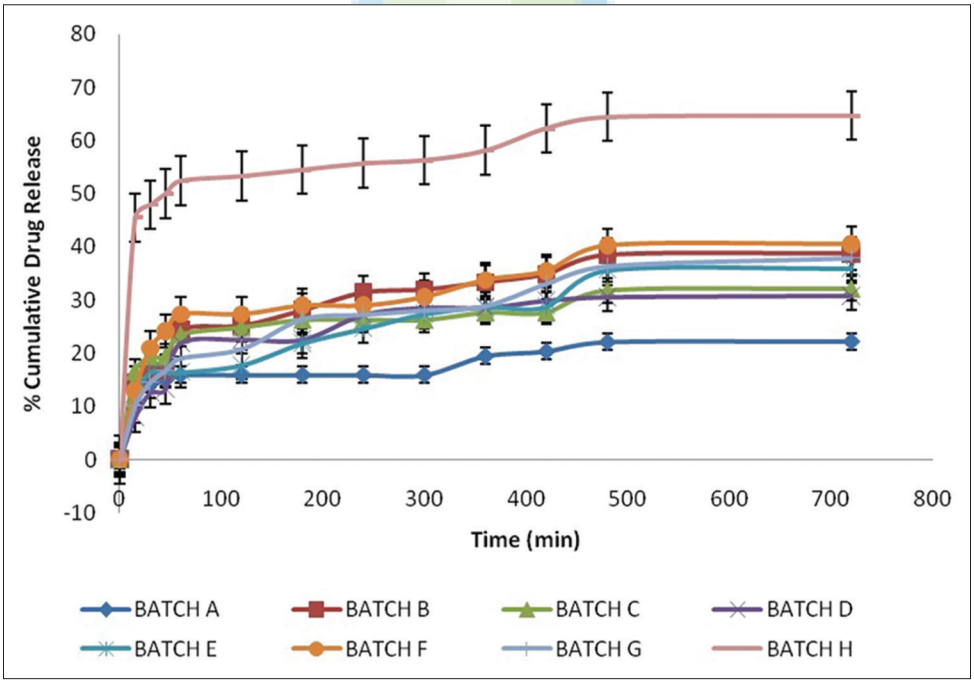

Figure 4: *In vitro* drug release study of nanoparticles formulations

Table 3: Experimental and predicted responses for optimized formulation (H)

Predicted			Observed		
Particle size (nm) (±SD, *n*=3)	DEE % (±SD, *n*=3)	% release (±SD, *n*=6)	Particle size in nm (±SD, *n*=3)	DEE % (±SD, *n*=3)	% release (±SD, *n*=6)
415.2±10.2	44±2.25	66.21±3.16	405.5±18.6	46.46±2.12	64.67±3.42

DEE: Drug entrapment efficiency, SD: Standard deviation

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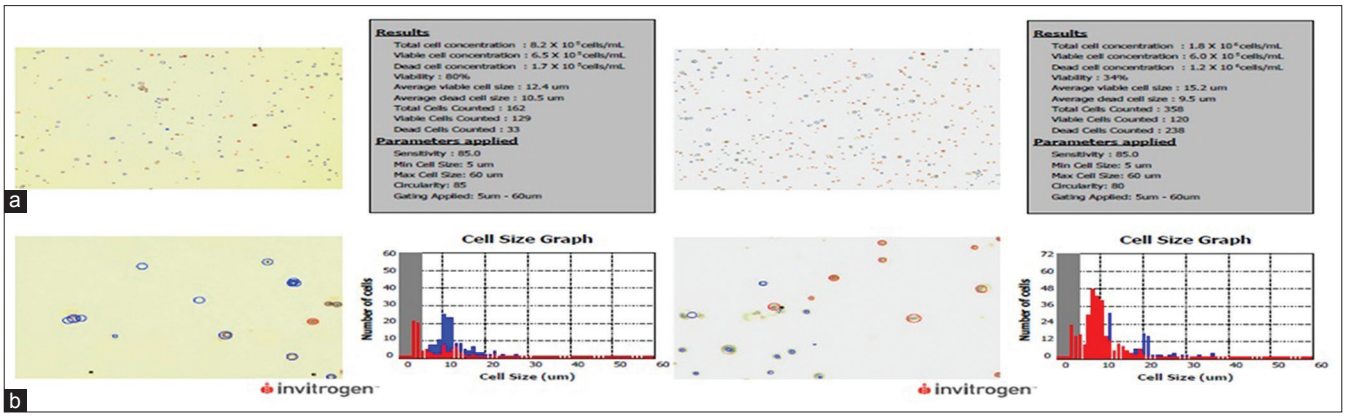

Figure 5: (a) Cell viability data for the control group (automated cell counter, INVITROGEN™) (b) Cell viability data for drug loaded nanoparticles treated group (automated cell counter, INVITROGEN™)

CONCLUSION

It may be concluded from the study that TSP may be suitable for formulation of mucoadhesive NPs for better efficacy and sustained delivery of anticancer drug irinotecan. This sustained release of irinotecan from the mucoadhesive NPs may enhance the efficacy of irinotecan and minimize the adverse reaction of drug on administration resulting in reduced toxicity.

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