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Research Article

Formulation and evaluation of antineoplastic drug loaded nanoparticles incorporated in sucralfate suspension as drug delivery system

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ABSTRACT

The main objective of the present work was to formulation and evaluatation of 5-Fluorouracil drug loaded nanoparticles incorporated in sucralfate Suspension as drug delivery system. 5 -Fluorouracil nanoparticles prepared by Nanoprecipitation method using sodium alginate as cross linking agent. Prepared nanoparticles were evaluated for drug entrapment efficiency, particle size, FTIR, DSC, TEM analysis and drug release studies. Based on above studies FN12 was selected as optimize formulation. Sucralfate suspension were prepared in order to select the best suspending agent concentration based on the evaluation test FS6 compositions were selected for incorporation of Nanoparticle. 5-Fluorouracil loaded nanoparticles incorporated in sucralfate suspension were prepared and characterized for various evaluation tests and FNS12 was optimized formulation to be selected. Comparative pharmacokinetic studies were carried for 5-Fluorouracil drug loaded Sucralfate Suspension and 5 -Fluorouracil loaded nanoparticles incorporated in sucralfate suspension and evaluated for various pharmacokinetic parameters. The results indicate the increase in $T_{1/2}$ and MRT in the in nanoparticles incorporated in Sucralfate suspension and sustain the drug release compare to Sucralfate Suspension. Histological examination revealed that there is a severe bleeding due to continuous use of 5-Fluorouracil Suspension observed within one week thus 5-Fluorouracil loaded nanoparticles incorporated in Sucralfate suspension (FNS12) was proved to be safe and effective for long term use.

Keywords: 5-Fluorouracil; Nanoprecipitation method; Sucralfate; Nanoparticles.

INTRODUCTION

Sucralfate is a non-absorbable, basic aluminum salt of a Sulphated disaccharide which has proven effective in the treatment of gastric and duodenal ulcers. Sucralfate forms polyvalent (Nagashima.*et al.,)* bridges to the positively charged proteins present in the mucosa and form past like, adhesive substances; a protective barrier is thus formed against further mucosal.(Nagashima, R.*et al*).

The major objective in designing nanoparticles incorporated sucralfate suspension as a drug delivery system Sucralfate acts as the cytoprotective and to carry the anti neoplastic drug loaded nanoparticles to the carcinoma site in the g.i.t which will cure carcinoma, enhance and to achieve successful targeted drug delivery, mucoadhesion and form a coating on inflamed cells, sustain release, localization of drug at carcinoma site (Peterson, D. *et al*.,).

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Materials: 5-Fluorouracil (5Fu) was obtained from Celone Pharmaceuticals Pvt. Ltd., India. Sodium alginate, PVP K30 and PVP K90 were purchased from S.D fine chemicals Mumbai India. Sodium carboxymethylcellulose, Xanthangum, Polaxomer407 were procured as gift samples from Cheminnova Remedies Pvt.Ltd, Methanol, was procured from Loba chemicals Mumbai, India. Acetonitrile and Methanol used are of HPLC grade, purchased from Ranbaxy Fine chemic. Sucralfate was purchased from Yarrow chem. Products (Mumbai), Ltd. Mohali. India. All other chemicals were of analytical grade and used without further purification. REMI R-2 research centrifuge was used for the separation of plasma from blood .Magnetic stirrer was used for dissolution assemble (RMEI, Electro techink, Ltd, Vasai, India).

Incorporation of 5-Fluorouracil loaded nanoparticles in to Sucralfate suspension:

Nanoparticles were prepared by Nanoprecipitation according to the method developed by Fessi and collegues (Fessi, H.*et al*.,). Nanoparticles were incorporated into sucralfate suspension as mentioned in previous literature (Arias, J.*et al*.,). Based on the previously performed *invitro* characterization for 5-Fluorouracil

Table 1: Pharmacokinetic Parameters of sucralfate suspension & 5-Fu nanoparticles

Pharmacokinetic parameters	FS6	FN12	FNS12
C_{max}	32±0.5773 (µg/ml)	20±0.2886 (µg/ml)	26±0.5 (µg/ml)
T_{max}	10±0.2516 (min)	14± 0.2886 (h)	9±0.251 (h)
Elimination rate constant(h^{-1})	0.5493±0.0023	0.68239±0.0062 (h^{-1})	0.13515±0.002(h^{-1})
Half Life	12.618±0.3477(min)	1.015763±0.04(h)	5.1285±0.264 (h)
AUC_{0-t}	60±0.5773	106±0.577	163±1
AUC_{0-inf}	90.909±0.528	18.875±0.223	18.875±0.1726
$AUMC_{0-t}$	5100±1	1843.2±3.109	2922±2
AUMC0-inf	161.8256±0.2779	43.2525±0.572	37.415±0.3066
MRT (h)	0.3726±0.5 (min)	2.4651±0.5 (h)	4.4054±1 (h)

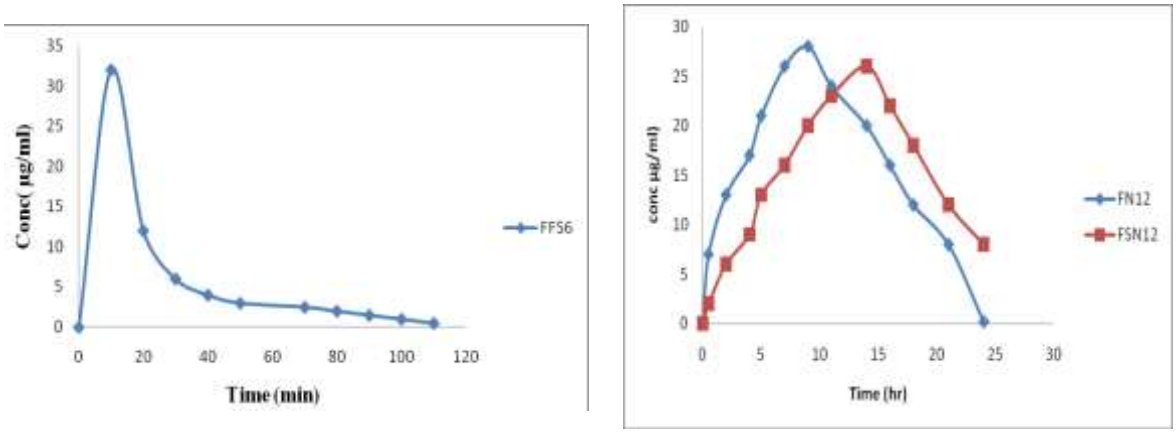

Figure 1: Pharmacokinetic parameters of 5-Fu suspension and nanoparticles incorporate in Suspension

nanoparticles (FN12), the best formulations of Sucralfate suspension based on the viscosity, sedimentation volume and redispersibility were selected .Considering the entrapment efficiency value accurately weighed 15 mg equivalent of 5-Fluorouracil nanoparticles were incorporated into Sucralfate suspension.

Extraction of procedure and analytical method validation in rat plasma:

Rats were classified into four groups with 6 rats in each group.

Group I: control with distilled drinking water and given corresponding normal saline daily by oral gavage.

Groups II and III: Treated with 0.1g/L of MNNG with distilled water prepared thrice per week for 24 weeks according to the protocol described in previous reports (M.Tatematsu *et al*., Li, S., Wang *et al*.,). The MNNG solution was protected from light and given ad libitum to rats through drinking water. At first six weeks, 1mL 10% sodium chloride was given to rats by oral gavage to enhance gastric cancer development [8]. From the 25th week to the 36th week, animals in Group II were treated in a manner similar to those in Group I, whereas rats in Group II were given Suspension was administered orally to the rats via a polyethylene cannula (diameter 2mm) with 1ml water under light ether anaesthesia, at a 5-FU dose equivalent to 15mg kg−1. This treatment was repeated daily for 7 day Blood samples (0.2 ml) were collected from the fossa orbitalis vein into heparinized tubes at the following time points: point10, 20, 30, 40, 50, 70, 80, 90, 100, and 120 min.(Rubinstein, A. *et al.,)*

Group III: Treated in a manner similar to Group II for 24 weeks thereafter treated with 5-FU drug loaded nanoparticles and Group IV were treated with 5-FU nanoparticles incorporated in Sucralfate Suspension Blood samples (0.2ml) were collected similar to that of Suspension from the following time points:0, 2, 5, 7, 9, 11, 14, 16, 18, 21 and 24 h .The heparinized blood samples were immediately centrifuged at 1000 *g* for 10 min in a research centrifuge, and the plasma separated and transferred to micro centrifuge tubes for storage at −20^{0}C.Frozen plasma samples were thawed. A 0.2mL aliquot transferred into a glass tube with a Teflon-lined cap, to which was added 0.2mL methanol. The mixture was vortexed for10 min and then centrifuged at 1000 g for 15min. The supernatant was then dried under a stream of nitrogen and resuspended in 0.1mL mobile phase, vortexed for 3 min and centrifuged at 1000 *g* for 5 min; 0.02 mL of the subsequent supernatant was subjected to HPLC for analysis of 5-FU as described below.

RESULTS AND DISCUSSION

5-Fu nanoparticles prepared based on the electrostatic interaction between sodium alginate and PVP (cationic effect) evaluated for various characterization tests .Nanoparticles thus formed are cationic with zeta potential ranges from (3.46±1.2 to 40±1.3), entrapment efficiency and particle size appears to be increase with increase in PVP concentration. *In-vitro* drug release

was performed for a period of 12 hr, drug release from all the formulations appears to release maximum amount of drug 85.33±1. Thus selected formulation subjected to freeze-dried and used for future incorporation. Sucralfate Suspension FS9 shows optimized sedimentation volume and good physical stability characters was used as a tool for nanoparticles were incorporated in to sucralfate suspension.

All the formulations prepared containing the therapeutic equal percentage of 5-Fluorouracil (15mg).In-vitro release was performed indicates all the formulation appears to release the drug with an intial lag time observed. FSN12 formulation appears to be the best of all formulations with highest percentage drug release at the end of 12 hr (91.2±0.6). Pharmacokinetic parameters such as Cmax , Tmax, Half life (T1/2) ,Elimination rate constant (h-1) , AUC 0-t , AUC 0-inf, AUMC 0-t, AUMC 0-inf, and MRT (mean residence time) were determined using PK1 and PK2 excel function for both 5-Fu suspension and 5-Fu nanoparticles and nanoparticles incorporated into sucralfate suspension data was displayed in table 1 .

From the results it was observed that Tmax of the 5-Fu loaded sucralfate suspension was 32±0.5773 and decreased in 5-Fu nanoparticles 20±0.2886 The elimination half life was extended in the 5-Fu nanoparticles incorporated in sucralfate suspension when compared with 5-Fu loaded sucralfate suspension and 5-Fu nanoparticles ie, 12.618±0.3477 minutes to 5.1285±0.264hr^{-1}.

CONCLUSION

The invention of this work understands recent advancements made in nanoparticulates incorporated in sucralfate suspension for better delivery of antineoplastic drugs at carcinoma site and improves the patient compliance.

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