Asian Journal of Chemistry Vol. 20, No. 8 (2008), 6125-6128

Formulation and Evaluation of 5-Fluorouracil Loaded Polymethacrylic Acid Nanoparticles

JAGDISH CHANDRA RATHI*, VAISHALI RATHI and S. TAMIZHARASI†
Department of Pharmaceutical Chemistry, NRI College of Pharmacy
Sajjan Singh Nagar, Bhopal-462 026, India
E-mail: roshan_rathi2005@yahoo.co.in

Nanoparticles represent a promising drug delivery system of controlled and targeted drug release. They are specially designed to release the drug in the vicinity of target tissue. Polymethacrylic acid nanoparticles containing 5-fluorouracil were prepared by emulsion polymerization method. SEM indicated that 5-fluorouracil nanoparticles have a discrete spherical structure without aggregation. The average particle size was found to be 263.66 ± 16.16–723.33 ± 15.27 nm. The particle size of the nanoparticles gradually increased with increase in the proportion of polymethacrylic acid polymer. The drug content of the nanoparticles was increasing on increasing polymer concentration. The *in vitro* release behaviour from all the drug loaded batches was found to be of zero order and provided sustained release over a period of 24 h.

Key Words: Nanoparticles, 5-Fluorouracil, Polymethacrylic acid, Novel drug delivery system.

INTRODUCTION

In recent years, there has been a considerable interest in the development of novel drug delivery system (NDDS) in order to modify and control pharmacokinetic behaviour of drug. Nanoparticles are colloidal polymer particles of a size below[1] 1 μm and hold promise as drug delivery for parenteral, peroral and ocular administration as well as adjuvant for vaccines[2-5]. Due to their greater stability and easier manufacturing, they offer advantages over other colloidal carriers such as liposomes and cell ghosts[6]. The major limitations of current anticancer drugs are their toxicity and lack of specificity[7]. The ideal dosage form in cancer chemotherapy is the one that provides a specific delivery of anticancer agent to the tumor site in sufficient amount for a long period of time with no interaction with normal tissue[8]. Colloidal drug delivery systems for targeted distribution of anticancer drugs are of increased interest for research in elevating the therapeutic efficacy of this class of drugs[9].

†Nandha College of Pharmacy, Perundurai Main Road, Erode-638 052, India.

5-Fluorouracil is an anticancer drug that is mainly used in the treatment of breast cancer and gastrointestinal tract (GIT) cancer. It has a very short biological half-life and requires frequent administration. However, frequent administration of drug may lead to severe side effects, such as mucosal ulceration in GIT, diarrhoea and even shock[10]. The aim of the present work was to prepare 5-fluorouracil nanoparticles and evaluate their physio-chemical properties.

EXPERIMENTAL

5-Fluorouracil was obtained as a gift sample from Biochem, Mumbai. Eudragit RL 100 was purchased from Rohm Pharma, Germany. Dichloromethane was procured from E. Merck Ltd., Mumbai. All other chemicals used were of analytical grade.

Preparation of nanoparticles: 5-Fluorouracil nanoparticles were prepared by emulsion polymerization method in continuous aqueous phase[11]. The polymethacrylic acid polymer was dissolved in dichloromethane and this solution was emulsified with the aqueous solution of 5-fluorouracil containing 2 % Tween 80 at 15 °C using a magnetic stirrer for 10 min. This solution was sonicated for 20 min at 15 °C. The nanoparticles formed were separated by fractional centrifugation. By following the above mentioned procedure four other batches of nanoparticles ratio of 1:0.5, 1:1, 1:2 and 1:3 were prepared and named as batch F_1, F_2, F_3 and F_4, respectively.

Estimation of drug content: Drug content was determined by incubating nanoparticles with 5 mL of ethanolic hydrochloric acid at 4 °C for 24 h. After 24 h incubation, the nanoparticles were separated by centrifugation at 3000 rpm and the drug content in the supernatant was analyzed by UV spectrometer at 226 nm.

Determination of particle size by scanning electron microscopy: Particle size was determined using scanning electron microscopy. The sizes of minimum of 100 particles were determined for average particle size.

***in vitro* Release study:** *in vitro* release studies were carried out by using dialysis tubes with an artificial membrane. The prepared 5-fluorouracil nanoparticles and 10 mL of phosphate buffer pH 7.4 was added to the dialysis tube and subjected to dialysis by immersing the dialysis tube to the receptor compartment containing 250 mL of phosphate buffer pH 7.4. The medium in the receptor was agitated continuously using a magnetic stirrer maintaining temperature at 37 ± 1 °C. Samples each of 5 mL of receptor compartment were taken at various intervals of time over a period of 24 h and each time fresh buffer was replaced. The amount of drug released was determined spectrometrically at 226 nm.

RESULTS AND DISCUSSION

5-Fluorouracil nanoparticles with different ratio of drug and polymer were prepared by emulsion polymerization method. The scanning electron microphotograph of 5-fluorouracil is shown in Fig. 1. It indicates that 5-fluorouracil nanoparticles have a discrete spherical structure without aggregation. The mean (± SD) size of drug loaded nanoparticles was found to be 263.66 ± 16.16 to 723.33 ± 15.27 nm. The particle size was gradually increasing on increasing the proportion of polymer. The drug content was determined by centrifugation method and it was found to be 41.73, 48.3, 56.3 and 54.06 % (w/w), respectively for the batch F_1-F_4 (Table-1) and formulation F_3 showed highest drug content.

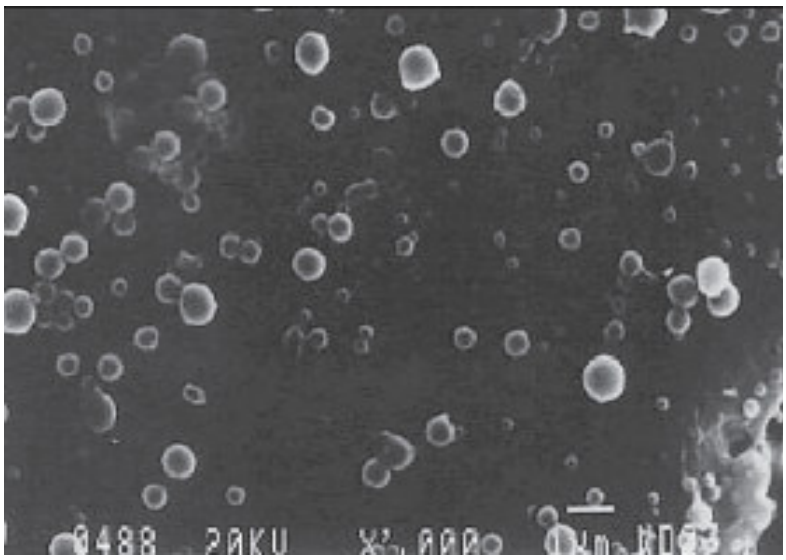

Fig. 1. Scanning electron microphotograph of 5-fluorouracil nanoparticles

TABLE-1
FORMULATION, PARTICLE SIZE AND DRUG CONTENT OF
5- FLUOROURACIL NANOPARTICLES

Batch code	Drug:Polymer ratio	Particle size* (nm)	Drug content* (% w/w)
F_1	1:0.5	263.66 ± 16.16	41.73 ± 1.160
F_2	1:1.0	330.66 ± 23.02	48.30 ± 1.170
F_3	1:2.0	436.66 ± 30.55	56.30 ± 0.818
F_4	1:3.0	723.33 ± 15.27	54.06 ± 1.440

*Average of three preparation ± SD

The *in vitro* release profile of 5-fluorouracil from different drug loaded nanoparticles is shown in Fig. 2. All the four batches of 5-fluorouracil nanoparticles exhibited sustained release for a period of about 24 h. All the drug loaded nanoparticles exhibited a biphasic release. The initial burst effect occurred within 1 h from all the drug loaded nanoparticles. The burst effect could be due to the release of drug loaded on the surface of nanoparticles and the remaining part of release may be due to slow diffusion of the drug from the nanoparticles matrix, by erosion. At the end of 24 h formulation F_1-F_4 released about 98.99, 95.11, 93.45 and 88.24 % of drug, respectively. The increase in polymer content exhibited a little variation in the cumulative release of drug.

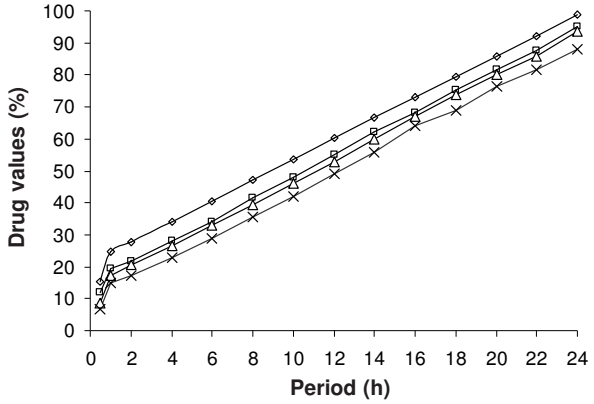

Fig. 2. *in vitro* Release study of various formulations F_1 (–◇–), F_2 (–□–), F_3 (–Δ–) and F_4 (–×–)

REFERENCES

1. J. Kreuter, *Pharm. Acta. Helv.*, **58**, 196 (1983).
2. M.N.V. Ravikumar, P. Singh and P.K. Dutta, *Indian Drugs*, **36**, 393 (1999).
3. S. Rani, R. Hiremath and A. Hota, *Indian J. Pharm. Sci.*, **61**, 69 (1999).
4. G. Cavallaro, M. Fresta, G. Giammona, G. Puglisi and A. Villari, *Int. J. Pharm.*, **111**, 31 (1994).
5. E. Lemos-Senna, D. Wouessadjewa, S. Lesieur, F. Puisieux, D. Duchene and G. Couarraze, *Pharm. Dev. Technol.*, **3**, 85 (1998).
6. J. Kreuter, *J. Control. Release*, **16**, 169 (1991).
7. T.K.M. Mbela, J.H. Poupaert, P. Dumont and A. Haemers, *Int. J. Pharm.*, **92**, 71 (1993).
8. T. Yoshikawa, S. Muranishi, C. Kato and H. Sezaki, *Int. J. Pharm.*, **8**, 91 (1981).
9. G. Mukherji, R.S.R. Murthy and B.D. Miglani, *Int. J. Pharm.*, **65**, 1 (1990).
10. Goodman & Gilmen's, The Pharmacological Basis of Therapeutics, McGraw Hill, NewYork, p. 1233 (1955).
11. M.E. Page-Clisson, H. Pinto-Alphandary, M. Ourevitch, A. Andremont and P. Couveur, *J. Control. Release*, **56**, 23 (1998).

(*Received*: 23 November 2007; *Accepted*: 1 July 2008) AJC-6657