Effect Of Neutron Activation Factor On The Physico-Chemical Properties Of Hydrophilic And Hydrophobic Polymer Formulation Of Matrix Tablets

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Abstract

This study was to investigate effect of neutron activation on the physicochemical properties and in vitro dissolution of sustained-release matrix tablets. The tablets incorporation of Samarium oxide (Sm_2O_3) and were compared before and after irradiation with thermal neutron for 5 minutes at 1.2×10^{12} neutron $cm^{-2}s^{-1}$. The neutron activation factor did not influence the compression properties of the tablets. The dissolution tests showed that irradiation increased the release of the model drug ketoprofen from the tablets. This effect might be explained by polymer degradation. Incorporation of Sm_2O_3 in the matrix tablets did not influence the release.

Keywords: Neutron activation; Matrix tablets; Sustained-release; Dissolution; Samarium oxide

Introduction

The oral route remains most preferred for drug administration because of its convenience to the patients. Solid dosage forms such as tablets or capsules are widely used to deliver the administered drugs. In most instances, these preparations are designed to release their drugs rapidly in the stomach. Some of the drugs irritate the stomach due their chemical properties. In order to protect the drug from the gastric juice and to prolong drug release, a sustained-release matrix system has been established as one way of delivering the drug. Sustained-release are tablets to dissolved slowly and release a drug over time. The advantages of sustained-release tablets are that they can often be taken less frequently than instant-release formulations of the same drug and that they keep a steadier therapeutic level of the drug in the bloodstream. Sustained-release tablets are able to control the release of drugs or to deliver the active ingredients to specific sites (Rang et al. 1995; Daeseleire et al. 2003; Giunchedi et al.2000). It is important to obtain information on the in vivo behaviour of these formulations following their administration to human subjects in order to ensure that the formulation perform correctly.

The conventional method of evaluating on oral dosage form in vivo involves measuring the plasma levels or urinary excretion of the drug over an appropriate time period. Such techniques give an indirect indication of the transit pattern, disintegration and dissolution behaviours of solid dosage forms within the gastrointestinal tract (GIT) i.e. the pharmacokinetic measurements indicate solely the results of drug release and not the responsible mechanisms. Although much about the performance of a system can be learned from in vitro release studies using conventional and modified dissolution, evaluation in vivo is essential in product development

Gamma-scintigraphy is applied extensively in the development and evaluation of pharmaceutical drug delivery systems. It is used particularly for monitoring formulations in the gastrointestinal and respiratory tracts. The radiolabeling is generally achieved by the incorporation of an appropriate technetium-99m or indium-111 labeled radiopharmaceutical into the formulation. In the case of complex dosage forms, such as matrix tablets or enteric-coated tablets, labeling is best undertaken by the addition of a non-radioactive tracer such as samarium-152 oxide or erbium-170 oxide followed by neutron activation of the final product. Systems investigated include tablets and multiparticulates for oral administration, enemas and suppositories, metered dose inhalers and nebulisers, and nasal sprays and drops. Gamma-scintigraphy provides information on the deposition, dispersion and movement of the formulation. The combination of such studies with the assay of drug levels in blood or urine specimens, pharmacoscintigraphy, provides information concerning the sites of drug release and absorption (Wilding et al. 1992; Ahrabi et al. 1999).

The objective of this study were to study the Physico-chemical properties of new formulation of pharmaceutical sustained-release tablet for one daily oral administration upon neutron activation and to study appropriate activity of radioactive tracer (Sm-153) in the dosage forms to fulfilled the requirement of gamma scintigraphy.

Materials and methods

Materials

Ketoprofen (Sigma-Aldrich, Germany), Samarium oxide (Aldrich, USA), phosphate buffer pH 7.4, hydrochloric acid, distilled water, Lactose monohydrate (Merck, Germany), Microcrystalline cellulose (Aldrich, USA), Polyvinylpyrolidone (Sigma-Aldrich, USA), Eudragit L100-55, HPMC (hydroxypropyl methylcellulose) and Magnesium stearate (Sigma-Aldrich, Germany).

Methods

All materials were sieved through 300 μm diameter to remove or break up lumps before mixing. Polymer and excipients was mixed using 3D mixer (China) for 15 minutes. The formulation was transferred into a planetary mixer (Kenwood, Malaysia) and water was added slowly until a fine granule is produce. The wet granules was screened through a 1.0 mm diameter sieve using an oscillator granulation machine (Kalkewa VDM4, India) and was dried in an oven at 60 ^{o}C (memmert, Germany) for 18 – 24 hours. After adding glidant and lubricant the tablet were compressed (7.0 mm diameter, concave punches) using 10-station rotary tablet machine (India) at a tablet weight of 200 mg. Each tablet contained 20 mg of ketoprofen, combination polymer of Eudragit L100-55:HPMC (30:30), MCC (10mg), PVP (10 mg), 5 mg of Sm_2O_3, 2mg of talc and mg stearate and lactose as a filler.

Radiolabelling and uniformity of the content of Sm_2O_3 in the cores

Three days before the study, tablets were irradiated for 5 min using TRIGA PUSPATI reactor at a neutron flux of 1.2 x 10^{12} n/cm^2/sec. The delay in used was allowed the decay of sodium-24

formed during the irradiation. At the time of administration each tablet was contained approximately 0.5 MBq samarium-153 (Wilding et al. 1992). The uniformity of Sm_2O_3 content was determined by ensuring that the samarium-153 activity using Neutron Activation Analysis (NAA).

In Vitro Dissolution Testing

The in vitro dissolution studies were carried out using apparatus type II (paddle apparatus, BP 2007). The dissolution medium consisted of 900 ml 0.1 M HCl with pH 1.2 for first 2 hours and the phosphate buffer pH 7.4 for 3 hours to 8 hours, maintained at 37 ± 0.5 ^{o}C of rotation 50 rpm using manual dissolution tester (ERWEKA DT 70, Germany) (BP 2007). The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu, Japan) at wavelength 288 nm.

Statistic

The data were evaluated using paired t test analysis method (GrapPad Prism program). A statistically significant difference was considered at $p < 0.05$.

Results

The uniformity of content for Sm_2O_3 in the tablet formulation was determined by radioactivity of Sm-153 (Table 1). The homogeneity within of Sm_2O_3 in tablet and in powder forms formulation was no significantly difference ($p = 0.05$).

Table 1: uniformity of the content of Sm_2O_3 after 3 days irradiation.

No	Radioactivity (MBq)	
	5 mg Sm-153 in powder forms	5 mg Sm-153 in matrix tablet
1	1.140	1.175
2	1.162	1.165
3	1.166	1.161

The tablet also tested for the physicochemical properties before and after irradiation time. The appearance of the irradiated sample was compared with non-irradiated samples and they were no colour changes during irradiation time.

The irradiation was not influence the physical properties of the matrix tablet due their weight variation, thickness, and hardness test based on BP 2007.

The influence of irradiation on the tablet was well demonstrated by the release of ketoprofen. The rate of release steadily released or not releases the ketoprofen during 2 hours in acid condition. However after transfer the tablets into phosphate buffer solution, tablets exposed to irradiation were increasing released the ketoprofen more than before irradiation (Fig. 1).

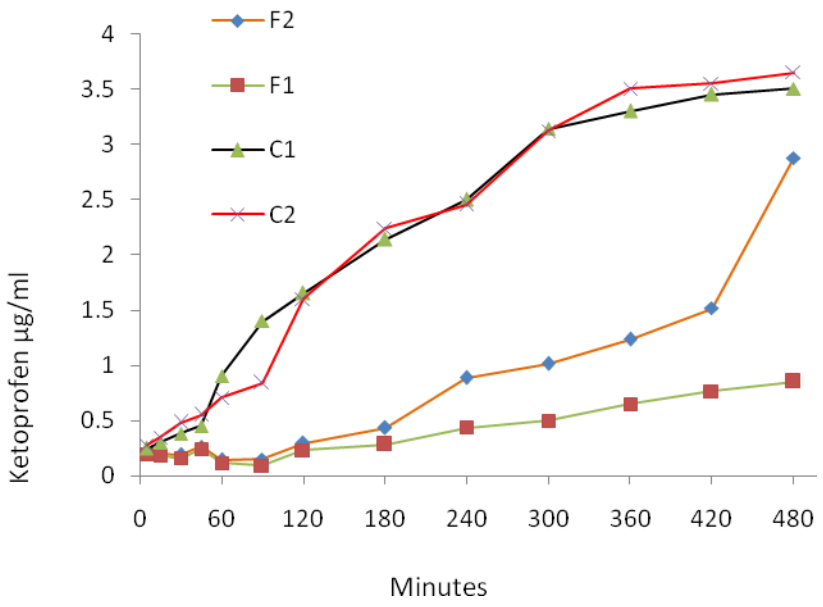

Fig. 1: Release profiles from matrix tablets in 0.1 M HCl (2 hours) and following in phosphate buffer (2-6 hours): F1-before irradiation (□), F2- after irradiation (◇), C1- control before irradiation (X) and C2- control after irradiation (△)

Discussion

The present study compared the in vitro characteristics of matrix tablets before and after irradiation. The irradiation affected the matrix formulation to a great extent, indicating physical / chemical changes of the matrix material. Drug release from tablets was increasing after exposure to irradiation (Waaler et al. 1999). However this procedure did not affect the dissolution pattern at all, proving that the observed effects were caused by the irradiation procedure alone.

According to the Waaler et al. 1999 found that ionizing radiation can be effects to the polymer depending on the chemical structure of the polymer, two reactions may be observed; cross-linking of the polymer chains, ultimately leading to the formation of an insoluble network or scission, resulting in a decrease in average molecular mass. The effect of neutron irradiation on the molecular mass was not determined in this study.

Conclusion

The dissolution tests showed that irradiation increased the release of the model drug ketoprofen from the tablets. This effect might be explained by polymer degradation. Incorporation of Sm_2O_3 in the matrix tablets did not influence the drug release from the matrix tablet.

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