Extended Abstract Journal of Clinical Medicine and Therapeutics 2020
Vol.5 No.2

Euro Pharmaceutics 2019: Studies on the influence of formulation and processing factors on the drug release from multiparticulate systems - KVRNS Ramesh - RAK Medical & Health Sciences University.

KVRNS Ramesh[1]

[1]RAK Medical & Health Sciences University, UAE

Abstract:
New technologies and methods are being developed for existing and new drug molecules to prepare sustained release (SR) and controlled release (CR) dosage forms. Multi-unit forms such as capsules offer significant benefits such as better control over drug release and less chances of dose dumping. In the present work, pellets of furosemide (as a model drug) are arranged by extrusion and spheronization. It belongs to BCS class IV drugs having poor solubility. Since furosemide presents low solubility in gastric fluids, to initiate a swift release from the pellets, a novel approach of incorporating the inclusion complex of furosemide in sulfobutyl ether cyclodextrin in the pellets was employed. Inclusion complex is prepared by kneading method. The effectiveness of almond gum as a binding agent in extrusion and spheronization was examined. Compared to pellets prepared by employing microcrystalline cellulose, the pellets made by using almond gum were noticed to be more uniform in size and revealed a more controlled release spread over 12 hours. The influence of various processing parameters such as speed of extrusion, rpm of spheronizer and time of operation was studied. The characteristics of pellets such as size, size distribution, and shape and drug release are influenced by formulation and processing variations. The drug release data proved a good fit into both Higuchi and Korsmeyer - Peppas equations. The differential scanning calorimetry and infrared spectroscopy (IR) studies revealed that there are no interactions between furosemide and almond gum. The x-ray diffraction studies indicated that the drug furosemide existed in amorphous state in the inclusion complex. The scanning electron microscope (SEM) images of pellets showed that the pellets have spherical shape and their size depended on amount of almond gum utilized. The details of experiments performed and results of the investigations will be presented.

Background:
Multiparticulate delivery systems are being increasingly recognized as more beneficial over single unit products because of more uniform distribution in gastrointestinal tract, less chance of dose dumping, better control on drug release, and more bioavailability with negligible variation among different individuals. Pellets are one commonly employed multi-particulate dosage form. New polymers need to be explored for their utility in palletization process. Objective: The goal of the investigation is to assess the feasibility of employing inclusion complex of poorly soluble drug furosemide in the design of slow-release pellets and investigate the usefulness of almond gum as a pelletizing agent. Materials and Methods: Inclusion complex of furosemide in sulfobutyl ether7-beta-cyclodextrin is prepared to enhance its dissolution. Pellets of inclusion complex are prepared by extrusion and spheronization employing almond gum as the spheronizing agent. The influence of almond gum proportion and speed of spheronization on the characteristics of pellets and drug release is investigated. Results: Inclusion complexation converted crystalline furosemide into an amorphous form, enhancing its dissolution. With changes in the percentage of almond gum and speed of spheronization, the size of the pellets could be varied which ranged from 640 to 1305 µ. Conclusion: Employing the inclusion complex of poorly soluble drugs for preparing SR pellets is a novel approach which ensures prompt, but slow-release spread over 12 h in the gastric fluids.

Materials & Methods:
Furosemide (gift sample from Julphar Gulf Pharmaceutical Industries UAE), SBE7 -β-CD (SBE7 -β-CD-Cydex Corp, USA); Almond Gum (Grade 1) is obtained from Hare Krishna Herbals, Kakinada, India. All other excipients, chemicals, and solvents are of analytical grade and were purchased commercially.

Inclusion Complexation Of Furosemide In SBE7 -B-CD Phase Solubility Study:
Phase solubility studies were done to know the molar ratio of dense formation between furosemide and SBE7 -β-CD as per the Higuchi and Connors method.[21] Excess amounts of furosemide were added to 15 ml of distilled water containing increasing concentrations of SBE7 -β-CD in 25 ml stoppered glass bottles. The resulting diffusions were shaken at 37 ± 0.5°C for 3 days in a temperature-controlled stirring water bath (SeichemTech SK 330 Pro). At the end of 3 days, sample dispersion was removed and after filtration through a 0.45 µm membrane, estimated spectrophotometrically at 271 nm (Shimadzu Model UV 1600) for the amount of furosemide soluble. Phase solubility studies were performed in triplicate. Solubility diagrams were drawn between the molar concentration of furosemide soluble and the molar concentration of SBE7 -β-CD. From the resulting plot, the stability constant for the establishment of complex between furosemide and SBE7 -β-CD was determined by employing the formula:
Ks = Slope/S0 (1–Slope)
The slope is calculated from the plot [Figure 1] and S0 is the equilibrium solubility of furosemide.

Preparation of inclusion complex:
The inclusion complexes of furosemide with SBE7 -β-CD were prepared by kneading (KN) and freeze-drying (FD) procedures in a 1:1 M ratio.

KN method:
The required quantities of furosemide and SBE7 -β-CD were accurately weighed, added to a mortar, and kneaded for 45 min.

This work is partly presented at 18th Annual Congress on Pharmaceutics & Drug Delivery Systems, June 27-28, 2019 at Amsterdam, Netherlands

While carrying out the KN, little quantity of methanol:water (20:80 v/v) solution was added to the kneaded mass to ensure sufficient consistency.

Conclusion:
The present study was taken up to determine the influence of formulation and processing factors on the drug release of furosemide pellets prepared by extrusion and spheronization. Drug release from pellets containing only the poorly soluble furosemide resulted in a poor release. Inclusion complexation of furosemide with sulfobutyl ether7-beta-cyclodextrin resulted in increased dissolution. FD method gave a complex with higher dissolution than the KN method. The pellets of furosemide complex could be prepared employing almond gum without the need for the conventional spheronizing agent MCC. With changes in the percentage of almond gum and speed of spheronization, the size of the pellets could be varied. As percentage of almond gum and speed of spheronization increased, the pellet size increased. With changes in almond gum percentage and size of pellets, extent of drug release also changed (F1 > F4 > F2 > F5 > F3 > F6). Employing the inclusion complex of poorly soluble drugs for preparing SR pellets is a novel approach which ensures prompt but slow release in the gastric fluids.

Acknowledgment:
The authors express their gratitude to the President of RAK Medical and Health Sciences University, UAE and Dean RAK College of Pharmaceutical Sciences for their encouragement and support in carrying out the research