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The Evaluation and Various Development of Mucoadhesive Microspheres System of Simvastatin

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Abstract – The objective of the present study was to prepare and evaluate the mucoadhesive microspheres of Simvastatin. Simvastatin microspheres were prepared by orifice-ionotropic gelation method using polymers such as HPMC (K 100 M), carbopol 940P, sodium CMC, guar gum, sodium alginate, ethyl cellulose, methyl cellulose and xanthan gum. Totally 15 different formulations of Simvastatin were prepared by using the above polymers. The microspheres were characterized for drug content, entrapment efficiency, mucoadhesive property by in vitro wash-off test and in-vitro drug release. The formulation F10 was selected as an ideal formulation based on the in vitro release profile which shows an extended drug release of 97.11% upto 8 hours in phosphate buffer of pH 7.0. Surface morphology (SEM analysis) and drug-polymer interaction studies (FT-IR analysis) were performed only for the ideal formulation, F10. The microspheres were smooth and elegant in appearance showed no visible cracks as confirmed by SEM and FT-IR studies indicated the lack of drug-polymer interactions in the ideal formulation, F10. The in vitro release data of all microsphere formulations were plotted in various kinetic equations to understand the mechanisms and kinetics of drug release. The ideal formulation, F10 followed Higuchi kinetics and value of "n," is calculated to be 0.86 indicated that the drug release shows non-Fickian diffusion.

The microspheres were evaluated for particle size and shape and surface morphology by SEM, drug loading, drug incorporation efficiency, In vitro mucoadhesion, and In vitro drug release study. Particle size was found to be in the range of 29.48 to 37.08 µm, which is favourable for intranasal absorption.

Mucoadhesion had been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs.

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INTRODUCTION

Mucoadhesive formulations orally would achieve a substantial increase in the length of stay of the drug in GI tract stability problem in the intestinal fluid can be improved. Mucoadhesive microsphere carrier systems are made from the biodegradable polymers in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery system. They have varied applications and are prepared using assorted polymers. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling Bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

To overcome the relativity short GI time and improve localization for oral controlled or sustained release drug delivery systems. The polymers which adhere to the mucin epithelial surface are effective and lead to significant improvement in oral drug delivery based on this three broad categories.

Simvastatin is anti hyperlipidemic used to control elevated cholesterol, or hypercholesterolemia. Simvastatin is a member of the statin class of pharmaceuticals, is a synthetic derivate of a fermentation product of aspergillus terreus. It is structural analog of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme). Like other agents, it

inhibits the enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase.

It has an extremely high affinity for this enzyme and was considered the most potent agent of the HMG-CoA class. Simvastatin is inactive lactone prodrug and hydrolyzed in the gastrointestinal tract to the active ß -hydroxy derivative. It decreases total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B, while increasing HDL.

In the present study, an attempt was made to develop mucoadhesive simvastatin microspheres by orificeionotropic gelation technique using polymers such as sodium alginate, HPMC (K 100 M), carbopol 940P, sodium CMC, guar gum, ethyl Cellulose, methyl cellulose and xanthan gum. The prepared microspheres were evaluated for drug content, entrapment efficiency, mucoadhesive property, surface morphology, drug polymer interaction and in vitro drug release studies.

MUCOADHESIVE MICROSPHERES OF SIMVASTATIN FOR NASAL DELIVERY

he nasal route has gained tremendous attention for systemic drug delivery by many researchers within the last few decades due to its great potential utility for drug delivery. It offers an attractive alternative for drugs that have limited oral bioavailability, are destroyed by gastrointestinal fluids, or are highly susceptible to hepatic first pass or gut wall metabolism. Nasal drug delivery also offers the convenience and safety of being noninvasive. However, the nasal route has limitations like mucociliary clearance, low permeability etc. Mucoadhesive preparations like microspheres have been developed to increase the contact time of the dosage form, thus enhance drug absorption and its bioavailability.

Simvastatin a anti hyperlipidaemic, HMG-COA reductase inhibitor is the drug of choice in the treatment of hypercholesterolemia and dyslipidemia. Simvastatin undergoes extensive first pass metabolism by oral route and thus exhibits only 5% oral bioavailability. The present investigation was aimed at avoidance of first pass metabolism of simvastatin by preparing chitosan microspheres for nasal administration. Mucoadhesive microparticle nasal delivery is an attractive concept in that the drug can entrapped inside particles to be released at nasal mucosal surface, where the particles are adhered due to their bio/ mucoadhesiveness. Extensive works on microspheres using mucoadhesive polymers for drug like pentazocine7, FITC-dextran8 reported.

Various biodegradable materials have been used as carriers for microparticulate drug delivery systems. Recently, chitosan microspheres have received considerable attention due to its biodegradability, biocompatibility, high charge density, toxicity and mucoadhesive property. The gelling property of chitosan offers diverse uses including microencapsulation and controlled release of drugs via microparticulate systems. Different methods have been tried by various researchers to prepare chitosan microspheres, e.g. ionotropic gelation10, emulsification-crosslinking, thermal crosslinking12, solvent evaporation13, spray drying and precipitation coacervation.

MUCOADHESIVE MULTIPARTCULATE DRUG DELIVERY SYSTEM OF SIMVASTATIN

For systemic delivery, the oral route has been the preferred route of administration for many drugs. When administered by the oral route, however, many therapeutic agents have been reportedly subjected to extensive presystemic elimination by gastrointestinal degradation and/or hepatic metabolism. The results of low systemic bioavailability, short duration of therapeutic activity, and/or formation of toxic and inactive metabolites have been often reported. Further, the quick passage of dosage forms through the absorptive segment of GIT often leads to unutilized drug, particularly in case of extended delivery of narrow absorption window drugs.

The mucoadhesive drug delivery systems are delivery systems which utilized the property of mucoadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time. The pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of the drug.

Simvastatin is an antihyperlipidemic drug with poor oral bioavailability (<5%) due to the first pass metabolism. The possible methods to avoid first pass metabolism include transversal, buccal, rectal and parenteral routes of administration. The oral route is the most commonly used and preferred route of choice for the delivery of drugs, although several factors like pH of GIT, residence time and solubility can affect the drug administration by this route. Simvastatin, a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After, oral administration, simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. The physiological properties of drug like short half-life (2 to 3 h), dose size (5 to 80 mg) and

low molecular weight (418.57) makes it a suitable candidate for formulation by mucosal route.3,4 The ionotropic gelation technique was selected to prepare the simvastatin loaded mucoadhesive microspheres due to its simplicity and low cost.The aim of the present study was to prepare and evaluate the mucoadhesive microspheres as a new oral controlled release system for simvastatin.

EVALUATION OF MICROSPHERES

Estimation of drug content - Initially, the microspheres were powdered using mortar and pestle. Then powder equivalent to 10 mg of Simvastatin was dissolved in 20 ml methanol and the volume was made up to 100 ml with pH7.0 phosphate buffer containing 0.5%SLS.

The Solution was filtered through Whatman filter paper no. 41 to obtain the stock Solution A. The Stock Solution A (1ml) was diluted to 10ml to obtain the stock Solution B . The absorbance7 of the resulting solution is observed at λmax 239nm using the U.V. Spectrophotometer(Lab . India).

Entrapment efficiency - Entrapment efficiency was calculated using the following formula:

$$\text{Bulk Density} = \frac{\text{Weight}}{\text{Volume}}$$

The flow property of microspheres was evaluated using Carr's Index.

$$\text{Carr's Index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

The angle of repose of the granules was determined by the fixed funnel and the free standing cone method.The Hausner ratio was estimated as :Hausner ratio=Tapped density /Bulk density.

In vitro wash off test for mucoadhesion - A 4-cm by 4-cm piece of sheep intestine mucosa was tied onto a glass slide using the thread. The microspheres were spread (∽ 100) onto the wet, rinsed, tissue specimen and the prepared slide was hung on to one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in the beakers containing the simulated gastric fluid USP (pH 1.2), and the pH 7.0 phosphate buffer. At the end of 30 minutes, 1 hour, and at hourly intervals up to 8 hours, the number of microspheres still adhering on to the tissue was counted.

$$\text{Mucoadhesive Property} = \frac{\text{No. of Mucoadhesive adhered}}{\text{No. of Microspheres applied}} \times 100$$

In-vitro drug release studies - Drug release study was carried out in USP paddle type dissolution test apparatus (Electro lab TDT-06L). A quantity of microspheres equivalent to 20 mg of Simvastatin was used for the test. The dissolution medium pH 7.0 phosphate buffer containing 0.5% sodium lauryl sulphate was used. The volume of the dissolution medium was 900ml, and the bath temperature was maintained at 37°C + 0.5°C. The microspheres were placed in the dissolution vessel and the vessel was covered, the apparatus was operated for 8hrs at 50 rpm. At definite time intervals the 5 ml of the dissolution fluid was withdrawn, filtered and again 5ml blank sample was replaced.The samples were analyzed spectrophotometrically at λmax 239 nm using a UV- spectrophotometer (Lab. India). All the studies were conducted in triplicate (n = 3).

Kinetics of drug release - The analysis of the drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of mucoadhesive controlled release systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, Higuchi and the Korsemeyer-Peppas equations. The order of drug release from the mucoadhesive microspheres was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the mucoadhesive controlled release systems was studied by using the Higuchi equation and the Korsemeyer - Peppas equation.

Fourier Transform Infrared Spectroscopy (FTIR) - There is always a possibility of drug - polymer interaction in any formulation due to their intimate contact. The technique employed in the present study for this purpose is FTIR spectroscopy. The FTIR spectra of Simvastatin, sodium alginate, methyl cellulose and F-10 formulation were obtained by the potassium bromide pellet method employing Bruker FTIR (ALPHA-T series). The scanning range used was 4400 to 500 cm^{-1} at a scan speed of 1 min.

Scanning Electron Microscopy(SEM) - The external surface morphology was evaluated under a scanning electron microscope (SEM-JEOL,JSM-840A, Japan). The microspheres were mounted directly on the SEM sample stub using the double sided sticking tape and coated with gold film (thickness 200nm) under the reduced pressure (0.001 mm of Hg). The voltage 5KV was used .

Differential Scanning Calorimetry (DSC) - The samples: pure drug alone (sample A),drug:sodium

alginate: methyl cellulose(1:2:1)physical mixture (sample B),optimized batch of microspheres, drug: sodium alginate: methyl cellulose(1:2:1)(sample C) were analyzed on DSC. The samples were heated from 40°C-280°C at a heating rate of 10°C/minute, under the argon atmosphere.

CONCLUSION

The ideal formulation F10. exhibited good mucoadhesive properties as indicated by in vitro wash off test. Simvastatin release from these mucoadhesive microspheres was slow and extended over up to 8h and depended on the composition of the coat. Drug release was diffusion controlled and followed Higuchi kinetics. These mucoadhesive microspheres are thus suitable for oral controlled release of Simvastatin. The FTIR studies ruled out the drug-polymer interaction in the ideal formulation, F10.

The microspheres of simvastatin (optimized formulation, drug-sodiumalginate-methylcellulose, 1 : 2 : 1 ratio)demonstrated oral controlled release of the drug for 8 hours and exhibited good mucoadhesive property. The FTIR and DSC studies revealed the absence of drug-polymer interaction. The SEM studies indicated the spherical shape of the microspheres. The formulated novel mucoadhesive multiparticulate drug delivery system of simvastatin can control the drug release, it has good mucoadhesive property and can improve the bioavailability of simvastatin.

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