Diclofenac As Microspheres

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Abstract

Diclofenac is currently the eighth largest-selling drug and the most frequently used NSAID (Non-steroidal anti-inflammatory drug) in the world, since its introduction in Japan in 1974. Diclofenac is among the better tolerated NSAIDs. Only major adverse effect of Diclofenac is that it causes direct and indirect irritation of the gastrointestinal tract (GIT). To reduce the side effects on gastrointestinal tract (GIT) and to improve therapeutic efficacy of Diclofenac, it can be formulated in polymeric microspheres. A brief review on why Diclofenac is incorporated into microspheres, the polymers that can be used, various methods of preparation are given in this review article.

INTRODUCTION

Non-steroidal anti-inflammatory drugs are usually abbreviated as NSAIDs, they reduce Pain, fever and inflammation. During the last few decades, there has been a substantial increase in the number of clinically available NSAIDs in the pharmaceutical market. NSAIDs annually account for 70 million prescriptions and 30 billion over-the-counter (OTC) medications sold in the United States alone [10] .

Diclofenac is in the class of Non-steroidal anti-inflammatory drug(NSAIDs), like most NSAIDs it act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A2). Prostaglandins act as messenger molecules in the process of inflammation.

Diclofenac is a Non-steroidal anti-inflammatory drug (NSAID) which is indicated in relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and also in relief of migraines, menstrual pain. Diclofenac is used commonly to treat mild to moderate post-operative or post-traumatic pain, particularly when inflammation is also present.

Diclofenac is among the better tolerated NSAIDs. The main adverse drug reactions associated with use of Diclofenac relate to direct and indirect irritation of the gastrointestinal tract (GIT).As awareness about this side effects increases so is the increase of research to reduce side effects. To reduce the side effects on gastrointestinal tract (GIT) and to improve therapeutic efficacy of Diclofenac, research is done to formulate Diclofenac in polymeric microspheres and a satisfactory result is found.

MATERIALS AND METHODS

Development of a new drug molecule is expensive and time consuming. So, it is better to improve safety efficacy ratio of an “old drug” by using different methods such as individualizing drug therapy and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, and targeted delivery are very attractive methods as they are less expensive and require lesser time [9] . Unlike most of the conventional Diclofenac formulation, Diclofenac formulated with microspheres have a longer half-life, which requires lesser dosing and thus increases the patient compliance. Microencapsulation of Diclofenac as microspheres for oral use has been employed to sustain the drug release and eliminate gastrointestinal tract irritation. Diclofenac incorporated with microspheres formulated as multi-particulate drug delivery systems spread out more uniformly in the gastrointestinal tract. This results improvement of drug absorption and reduces local irritation when compared to single-unit dosage form of Diclofenac [11] . Hence the therapeutic and patient compliance increases significantly.

MICROSPHERES

Microspheres can be described as small particles (1~1000μm) for use as carriers of drugs and other

therapeutic agents. We can define microspheres as, "A monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles". Microsphere based drug delivery systems have received considerable attention in recent years in pharmaceutical science.

COMMONLY USED POLYMERS

Diclofenac have been formulated into microspheres using biodegradable and non-biodegradable polymers and various methods for oral applications. To be successfully used in controlled drug delivery formulations, a material must be chemically inert. It must also have an appropriate physical structure, with minimal undesired aging, be readily process-able, should not invoke an inflammatory or toxic response, is metabolized in the body after fulfilling its purpose, leaving no trace, is easily process-able into the final product form, and must have acceptable shelf life. The molecular weight and viscosity of the polymer solution are the critical parameters in the preparation of microspheres.

Figure 1

Table_1: Polymers that can be used in formulating Diclofenac as follows

ACTIVE INGREDIENT	MICRO ENCAPSULATION TECHNIQUE	POLYMER	AIM
Diclofenac sodium	Solvent evaporation	Polymerized rosin	Sustained Release(**SR**)
	Solvent evaporation	Eudragit RL	Sustained release(**SR**)
	Phase separation Co-acervation using cyclohexane.	Ethyl cellulose	Controlled release(**CR**)
Diclofenac	Oil in oil(O/O) Emulsion solvent evaporation	Poly(1-lactic acid), copoly(lactic acid/glycolic acid)	Modified release(**MR**)
	A non-aqueous emulsion method	Ethyl cellulose, oloxamer-188, Hydroxyl Propyl Methyl Cellulose Phthalate.	Sustained release(**SR**)

METHODS OF PREPARATION

Micro particulate drug delivery technology represents one of the frontier areas of pharmaceutical science, which involves multidisciplinary scientific approach, contributing to human health care. The major micro-encapsulation technique which can be employed in formulation of Diclofenac incorporated in microspheres is briefly discussed below:

A) EMULSION SOLVENT EVAPORATION:

The polymer and drug were co-dissolved in water-immiscible organic solvent. The organic solution was poured into the aqueous phase containing 0.25% w/v poly viny1 alcohol. The resulting O/W emulsion was agitated continuously for 90 minutes at room temperature and under ambient pressure. The microspheres were collected by filtration, washed with de-ionized water, and dried. The dried spheres were passed through a 60 mesh stainless-steel sieve and stored at room temperature [21] .

B) CO-ACERVATION METHOD:

This method is simple and utilizes aqueous system for the preparation. This process consists of 3 steps under continuous stirring. The steps are:-

Formation of three phases, then:

Dispersing a core material in a solution of coating polymer.

Immiscible polymer in liquid state. (Coating material phase).

Coating is accomplished by controlled physical mixing of coating solution and core material in liquid manufacturing vehicle phase.

Rigidisation could be achieved by thermal, chemical crosslinking or desolvation techniques.

Recently controlled-release egg albumin-chitosan microspheres containing Diclofenac as a model drug was successfully prepared in laboratory by co-acervation method and a satisfactory result is found [6] .

RESULTS AND DISCUSSION

Oral Diclofenac cause gastrointestinal disturbances at a high incidence, which is an obstacle in increasing doses to obtain sufficient therapeutic effect. More over parenteral Diclofenac are required to maintain a certain level of blood concentration. Formulation of Diclofenac with microspheres for parenteral administration is satisfactory as they can avoid the contact with GI tract, resulting in enhanced effect with less dose of drug. Hence GI irritation can be avoided and this also requires lesser dosing thus increases the patient compliance. It is possible to achieve slow delivery of active drug, delivery of active drug at controlled rate, and targeted delivery by formulating Diclofenac as microspheres for oral preparation.

In recent time some in-vivo studies are conducted to learn about the pharmacokinetic and pharmacodynamic behavior

of the drug after microencapsulation of Diclofenac. Determination of Pharmacodynamics of NSAIDs (In this case Diclofenac) is usually done in laboratory by injecting the drug formulated with microspheres into the knee joints of adjuvant induced arthritic laboratory animals.

Chandrashekar G et al reported controlled-release parenteral formulations of Diclofenac sodium, for intra-articular administration. For in vivo studies, Technetium-99m labeled polyclonal human immuno-gamma-globulin was used as the radiopharmaceutical to demonstrate arthritic lesions by gamma-scintigraphy. Evaluation of arthritic lesions post-therapy in rabbits showed no significant difference in the group treated with PLGA incorporated with Diclofenac sodium compared to the control groups [20] .

Tuncay M et al prepared and evaluated albumin microspheres loaded with Diclofenac sodium. The microspheres so prepared were injected directly to the knee joints of laboratory test animals after the induction of arthritis in knee joints and the therapeutic efficacy of the formulations were found to be greater than the plain drug [3] .

CONCLUSION

From this review article it is clear that polymeric microspheres are found as a good candidate for the drug delivery systems of Diclofenac. But unfortunately the safety profile of these drug delivery systems for Diclofenac is not reported extensively so we can say that they are the best drug delivery system for Diclofenac. But most of the studies conducted in-vitro/in-vivo mediums shows satisfactory results. So, we may conclude they are promising drug delivery system for Diclofenac at this time.

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