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REVIEW ARTICLE

SITE SPECIFIC DELIVERY OF ANTI-ARTHRITIC DRUG BY GELATIN SURFACE MODIFIED BOVINE SERUM ALBUMIN MICROSPHERES

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Abstract

Non-steroidal anti-inflammatory drugs are the most commonly used and widely prescribed drugs all over the world. With the wide advantages, they are also associated with severe Gastro-Intestinal side effects. Developments of novel drug delivery systems have always been a challenge to formulation scientists because of their high instability and economic factor compared to the conventional dosage forms. Thus, the main objective of this review is to present an alternative way of developing NSAIDs as microspheres specifically using albumin polymers, which are playing an increasing role as drug carriers in the clinical setting. Hence, there is a prolonged release of the drug along with minimized side effects. A brief overview of the methods developed for the preparation of albumin microspheres and the most suitable techniques for optimum entrapment of drug have been emphasized. The in-vitro evaluations are also explained. In order to appreciate the medical application possibilities of albumin microspheres in novel drug delivery, some fundamental aspects are also briefly discussed.

Introduction:-

Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage. Immune complexes composed of IgM activate compliment and release cytokines which are chemotactic for neutrophils. These inflammatory cells secrete lysosomal enzyme which damage cartilage and erode bone, while PGs produced in the process cause vasodilation and pain. It is a chronic disorder for which there is no known cure.

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac is a newer derivative of diclofenac having less gastrointestinal complication. The usual therapeutic dose and dosing frequency of conventional aceclofenac tablets is high (100 mg twice daily), because of the short biological half-life of the drug (3-4 h), it is an ideal candidate for modified release dosage forms. To reduce the frequency of administrations and to improve patient compliances, once daily sustained release dosage forms of aceclofenac is desirable. (Chandiran *et al.*, 2010)

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other

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conditions, such as cancer and cardiovascular disease. NSAIDs are generally indicated for the symptomatic relief of the following conditions:

- Rheumatoid arthritis
- Osteoarthritis
- Inflammatory arthropathies (e.g ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Acute gout
- Dysmenorrhoea (menstrual pain)
- Metastatic bone pain
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury
- Pyrexia (fever)
- Ileus
- Renal colic
- They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth.

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane -A. In 2001, NSAIDs accounted for 70,000,000 prescriptions and 30 billion over-the-counter doses sold annually in the United States. (Green *et al*., 2001)

Gastric residence time (GRT) is an important parameter which may affect drug bioavailability of dosage forms. Many Drug Suffer from low bioavailability because of short gastric emptying time. Gastro retentive systems are the current approach to overcome the above problem of GRT. Among the number of approaches, mucoadhesive drug delivery system (FDDS) is one of the promising delivery system which adheres to the mucous layer of the stomach and thus remains in the stomach for long period of time.

In one such research study carried out by Chaturvedi *et al*., efforts were directed to reduce the side effects of Aceclofenac and to extend the release time using synthetic polymers. Different microsphere formulations loaded by Aceclofenac were obtained and fully characterized for morphology, size, encapsulation efficiency and release rate of Aceclofenac. (Chaturvedi *et al*., 2012).

Microspheres:-

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. (Kataria *et al.,* 2010).
Microspheres are homogeneous, monolithic particles which improve the treatment by providing localization of the drug at the site of action and by prolonging the drug release. The objective of the present study was to formulate sustained release microspheres of aceclofenac using egg albumin as release retarding agent. (Rajamanickam *et al*., 2010).

What is albumin and why albumin microspheres?
Albumin is a major plasma protein constituent, accounting for ~55% of the total protein in human plasma. Since they were first described by Kramer, albumin microspheres have been extensively investigated in controlled release systems as vehicles for the delivery of therapeutic agents to local sites. The exploitable features of albumin include its reported biodegradation into natural products, its lack of toxicity, and its non-antigenicity.

Albumin microspheres are metabolized in the body, and the size of particles, degree of stabilization, and site of metabolism are the main factors influencing the extent of metabolism. Drug release from the microspheres can be widely modulated by the extent and nature of cross-linking, size, the position of the drug, and its incorporation level in the microspheres. Colloidal forms of albumin have been considered as potential carriers of drugs for their site-specific localization or their local application to anatomically discrete sites. Albumin has been used as a carrier for targeting drugs to tumors, and since the synovium of the rheumatoid arthritis patients shares various features observed in tumors, albumin-based delivery systems can be used to target drugs to the inflamed joint. Intravenous administration of the drugs coupled with albumin has been reported to improve the targeting efficiency of the drug to arthritic regions. (Hilpert *et al.,* 1989). The circulation half-lives of the drugs have been reported to dramatically

increase when the drug is conjugated with albumin. Increasing the circulation half-life of the formulation by reducing its uptake by the reticuloendothelial system has been shown to improve the targeting efficiency of the formulation to the arthritic paws of rats. There are several reports on the use of long circulating liposomes to target the drugs to the arthritic joints. However, there are only a few reports on the use of microspheres for targeting the drugs to the arthritic joints. (Thakkar *et al.*, 2005).

Advantage and disadvantage of NSAID loaded albumin microsphere

The following advantages make them a promising means for the delivery of NSAIDs.

- Albumin Microspheres provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Albumin microsphere morphology allows a controllable variability in degradation and drug release.
- Reduces GI toxic effects.
- Albumin has non-antigenic property and ability to control the physicochemical characteristics of the microspheres produced, depending on the cross-linking methods and characteristics of cross-linking agent. (Jeevana *et al.*, 2009).

Some of the Disadvantages were found to be as follows:-

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.
- Larger size of extended release products may cause difficulties in ingestion or transit through the gut.
- Possibility of distal intestinal toxicological manifestations because of sustained release and enteric coated NSAID formulations. (Kataria *et al.*, 2011).

Methodology:-

Technologies used for prepare albumin microspheres:-

The preparation of microsphere from natural polymers involves three steps:-

1. The solution of the polymer is dispersed in a continuous medium such as vegetable oil or an organic solvent using a suitable cross- linking agent.
2. It involves separation of the solid microsphere formed, by filtration, centrifugation or freeze-drying.
3. Purification (to remove the residual solvents, surfactant and other additives) and drying (air dried, vacuum dried, freeze dried). (Liggins *et al.*, 2004).

Single emulsion technique:-

The micro particulate carriers of natural polymers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride etc. (Linda *et al.*, 2009). Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation3 The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release, and bio performance of the final multiparticulate product. (Kataria *et al.*, 2010).

Multiple emulsion / Double emulsion method :-

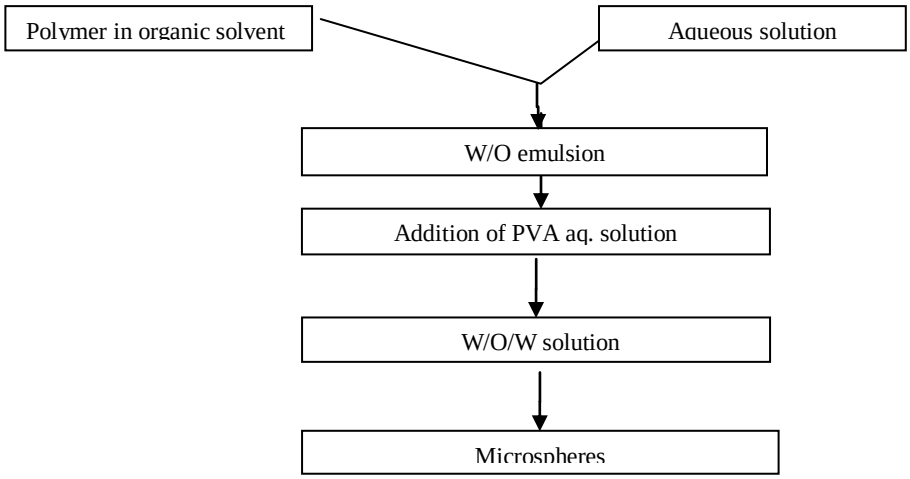

Figure 1:- Multiple emulsion / Double emulsion method

Emulsion solvent evaporation:-

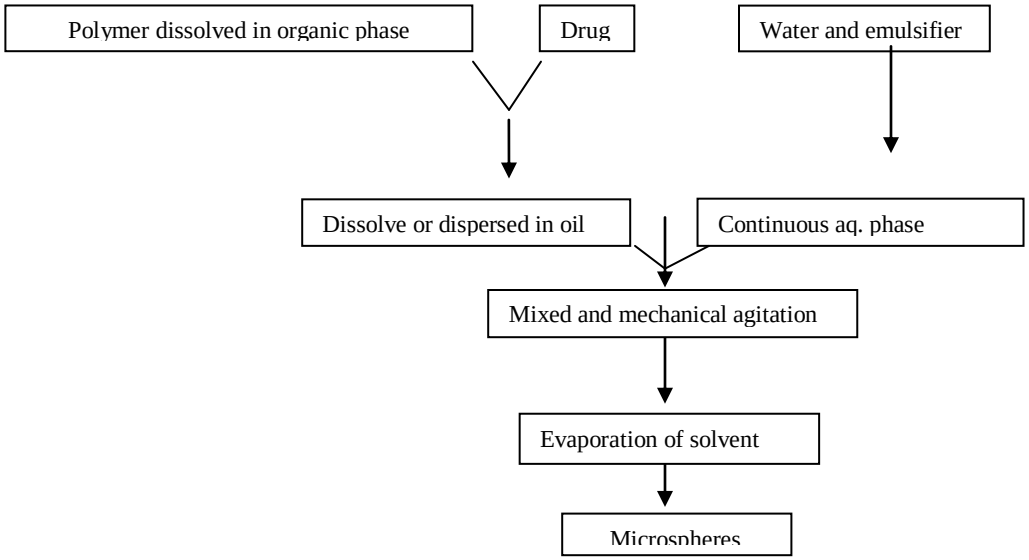

Figure 2:- Emulsion solvent evaporation

Emulsion cross-linking method:-

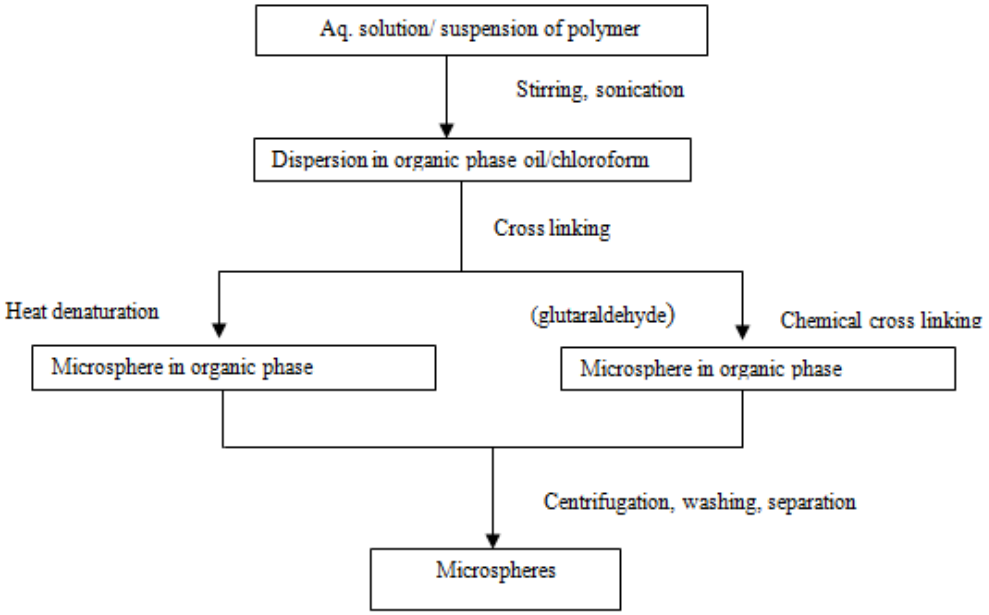

Figure 3:- Emulsion cross-linking method

Spray drying and spray congealing technique:-

Spray drying and spray congealing method are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or the cooling of the solution the two processes are named spray drying and the spray congealing respectively (Ying *et al*., 2007). Spray drying technique involves dispersing the core material in a liquefied coating material and spraying the core-coating mixture in to the environment to effect solidification of coating. Solidification is accomplished by rapid evaporation of the solvent in which coating material is solubilized. The process control variables in this technique are feed material properties, feed rate, method of atomization and drying rate. Spray drying method is rapid, reproducible and easy to scale up. But due to the fast drying process the polymer may lose its crytallinity and leads to the formation of porous microparticles. (Mathew *et al*., 2007).

Coacervation method:-

This method is simple and utilizes aqueous system for the preparation. This process consists of three steps under continuous stirring.

The formation of three phases:-

- Core material
- Dispersing a core material in a solution of coating polymer
- Immiscible polymer in liquid state (Coating material phase)

1. Coating is accomplished by controlled physical mixing of coating solution and core material in liquid manufacturing vehicle phase. (Muvaffak *et al*.,2004)
2. Rigidisation could be achieved by thermal, chemical cross-linking or desolvation techniques.

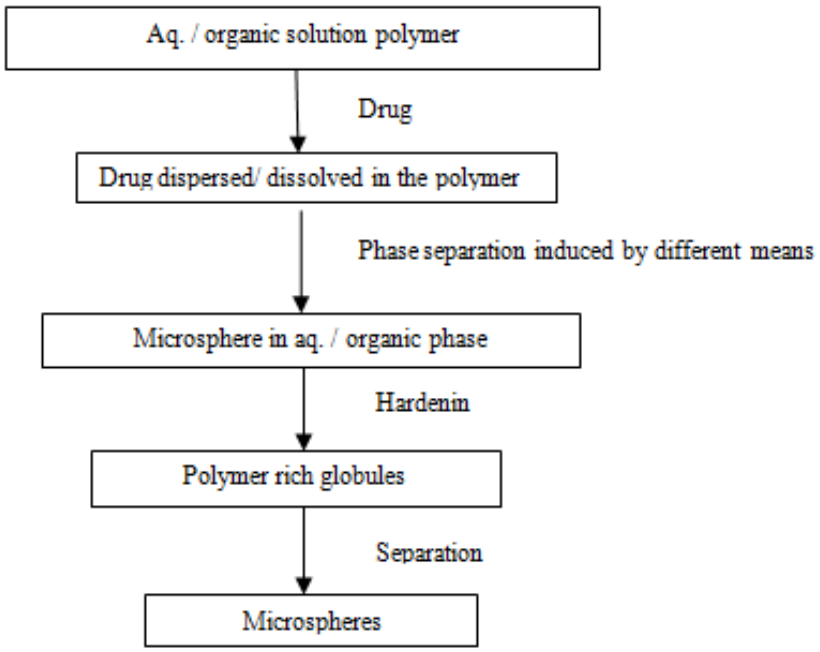

Figure 4:- Coacervation phase separation method. (Ghosh *et al.,* 2008).

Emulsification-heat stabilization technique:-

Emulsification-heat stabilization technique was carried out the preparation and characterization of albumin microspheres encapsulated with propranolol HCl by emulsion-heat stabilization technique. Bovine serum albumin microspheres (BSA) containing propranolol HCl were prepared by emulsification-heat stabilization technique. Briefly, a 5% solution of BSA containing 0.1% Tween80 was made, to which 4% propranolol HCl was added and used as the aqueous phase. The oil phase composed of 30 ml maize oil and 10 ml petroleum ether with 1% Span 80 as emulsifier were mixed together and allowed to stir for 10 min at 1000 rpm. The aqueous phase was added drop wise to the oil phase and stirred on a magnet stirrer at 1000 rpm for 30 min to form the initial emulsion. (Eroglu *et al*., 2000). This emulsion was then added to 40 ml of maize oil preheated to 120° C and stirred at 1000 rpm for 15 min to allow the formation and solidification of microspheres. The microsphere suspension was centrifuged at 3500 rpm for 30 min and the settled microspheres were washed three times with ether to remove traces of oil on microsphere surfaces. (Rathod *et al.,* 2008). The microspheres were vacuum dried in a desiccator overnight and stored at 4°C in dark. The microspheres had mean diameters between 1-25 µm of which more than 50 percent were below 5 µm. The encapsulated drug was found to be about 9% w/w of that initially added to microspheres and the superficial drug was 25% of the total amount of the encapsulated drug. Also albumin microspheres were noted to possess good bio-adhesion in such a way that about 70% of microspheres remained adherent on the surface mucosa of rat jejunum. The total amount of drug released from microspheres after 12h was 70%. (Sayyed *et al.,* 2003).

Sonication technique:-

As the technique name itself is self-explanatory, it just involves a simple sonication for certain period of time till a desired size of albumin microspheres is obtained. The albumin solution of desired concentration is taken which is sonicated. To this add the drug which will then form intrachain cross-link with cysteine residues of albumin chains (Cheng *et al.,* 2004).

Evaluation of microspheres:-

Some of the evaluation characteristics considered for albumin microspheres are as follows:

Drug Polymer Interaction Studies:-

IR spectroscopic studies:-

The IR spectra of the free drug and the microspheres were recorded. The identical peaks corresponding to the functional groups and albumin (BSA, Egg albumin, Human serum albumin) features confirm that neither the polymer nor the method of preparation has affected the drug stability. (Deepa *et al.,* 2012).

Particle size:-
Average particle size of microspheres was measured by optical microscopy. (Prasad *et al.,* 2011).

Percentage yield:-
Prepared microspheres were weighed after drying, and percent yield was calculated by help of this formula. The yield was calculated as the weight of the microspheres recovered from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100. (Patel *et al., 2013*).
% yield = Yp / Yt × 100
Where, Yp =Practical yield,
Yt = Theoretical yield.

Drug entrapment capacity:-
The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheress to lysate. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation-
PDE =Practical drug content/theoretical drug content x 100 (Nikam *et al.,* 2012)

Morphology/Electron microscopy:-
The morphological study of microspheres was done by scanning electron microscopy (SEM.). (Tuncay *et al.,* 2000).

In vitro release studies:-
In-vitro release studies can be performed according to USP XXII type I dissolution apparatus at suitable pH conditions. The temperature should be maintained at 37±0.5°C and the rotation speed of 100 rpm. Then 5 ml of sample should be withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample can be analyzed spectrophotometrically at specific wavelength (nm). (Jayaprakash, *et al., 2009*).

Conclusion:-
It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumours, detecting biomolecular interaction etc. So in future microspheres will have an important role to play in the advancement of medicinal field.

References:-
1. Chandiran SI, Sivakumar T, Kumar BP. (2010): Preparation and evaluation of aceclofenac loaded biodegradable Microspheres. International Journal of Pharmaceutical and Biomedical Research., 2(4): 19-23.
2. Chaturvedi S, Sharma PK, Visht S, Tyagi S. (2012): Comparison of emulsification and Ionic Gelatin method of Preparation of mucoadhesive Microsphere. The Pharma Innovation., 1(5): 1-9.
3. Deepa B, Satinder K, Ramandeep S, Ujjwal N. (2012): Magnetic microspheres as a targeted drug delivery system. Journal of Acute Disease., 1(2): 1-17.
4. Eroglu H, Suheyla K, Oner L, Sargon M, Hincal AA. (2000): Preparation of Bovine Serum Albumin Microspheres Containing Dexamethasone Sodium Phosphate and the in Vitro Evaluation. Turk J Med Sci., 30: 125–128.
5. Ghosh A, Nayak UK, Rout P, Nag T, Roy P. (2008): Preparation, Evaluation and in vitro- in vivo Correlation (IVIVC) study of Lamivudine Loaded Microspheres. Research J. Pharm. and Tech., 1(4): 353-356.
6. Green GA. (2001): Understanding of NSAIDs from aspirin to COX-2. Clin Cornerstone., 3(5): 50-60.
7. Hilpert LP, Mattrey RF, Mitten RM, Peterson T. (1989): IV injection of air filled Human albumin microspheres to enhance aterial Doppler signal: A preliminary study in rabbits. AJR., 153: 613-616.
8. Jayaprakash S, Mohamed SH, Mohamed PUF, Kulaturanpiallai A, Nagarjan M. (2009): Preparation and evaluation of biodegradable microspheres of methotrexate. Asian J Pharm., 3: 26-29.
9. Jeevana JB, Sunitha G. (2009): Development and evaluation of Gelatin microspheres of Tramadol Hydrochloride. J Young Pharma., 1(1): 24-27.
10. Kataria S, Middha A, Sandhu P, Bilandi A and Kapoor B. (2011): Microsphere: a review. International Journal of Research in Pharmacy and Chemistry, 1(4): 1184-1197.

11. Liggins RT, Burt HM. (2004). Paclitexal loaded poly L-Lactic acid microsphere properties of microsphere made with low molecular weight polymer. Int. J. Pharm., 222(1): 19-33.
12. Linda SL, Paul TS, Hard AD. (2009): Burt HM. Intra-articular treatment of inflammatory arthritis with microspheres formulations of methotrexate: pharmacokinetics and efficacy determination in antigen- induced rabbits. Inflammation research, 58: 445-456.
13. Mathew TS, Gayathri DS, Sandhya KV. (2007): Formulation and Evaluation of Ketorolac Tromethamine-loaded Albumin Microspheres for Potential Intramuscular Administration. AAPS Pharm Sci Tech., 8(1): 1-9.
14. Muvaffak A, Gurhan I, Hasirci N. (2004): Prolonged cytotoxic effect of colchicine released from biodegradable microspheres. J Biomed Mater Res Part B: Appl Biomater. 71: 295-304.
15. Nikam KV, Gudsoorkar VR, Hiremath SN, Dolas RT, and Kashid VA. (2012): Microspheres - A Novel Drug Delivery system. International journal of pharmaceutical and chemical sciences, 1: 113-128.
16. Patel S, Chand T and Maulik T. (2013): Formulation Development and Evaluation of Microsphere Containing Duloxetine Hydrochloride. International Journal of Research in Pharmaceutical and Biomedical sciences, 4: 568-572.
17. Prasad BS, Giri, Setty C.M.,Gupta V.R.M., Devanna D.,and M. Devi Rama. (2011): Aceclofenac-Loaded Alginate Microspheres Prepared By Ionotropic Gelation Method: Effect of Formulation Variables on Encapsulation Efficiency, Morphology and Release Characteristics, 3(2): 10-24.
18. Rajamanickam D, Rajappan M, Varadhrajan M, Srinivasan B. (2010): Formulation evaluation of albumin microspheres containing Aceclofenac. International Journal of Pharmaceutical Sciences Review and Research, 4: 112-117.
19. Rathod S, Deshpande SG. (2008): Albumin microspheres as an ocular delivery system for pilocarpine nitrate. Indian J. Pharm. Sci., 70 (2): 193-197.
20. Sayyed B, Sajadi T, Naheed R. (2003): Preparation and characterization of albumin microspheres encapsulated with propranolol Hcl. DARU., 11(4):137- 141.
21. Thakkar H, Sharma RK, Chuttani K, Murthy RR. (2005): Albumin Microspheres as carrier for Antiarthritic drug celicoxib. AAPS Pharm Sci Tech., 6(1): 65-73.
22. Tuncay M, Calis S, Kas HS, Ercan MT, Peksoy L, Hincal A. (2000): Diclofenac sodium incorporated PLGA (50:50) microspheres formulation considerations and in-vitro/in-vivo evaluation. Int J Pharm., 195:179-188.
23. Ying LU, Zhang G, Sun D, Zhong Y. (2007): Preparation and evaluation of biodegeradable flubiprofen gelatin microspheres or intra-articulate administration. Journal of microencapsulation, 24(6): 515-524.