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FORMULATION AND CHARACTERIZATION OF MICROSPHERE OF LORNOXICAM

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Abstract:

Sustained release polymeric microspheres of lornoxicam are prepared by using fluidized bed processor using polysaccharide as a polymer In vitro dissolution studies in acidic and neutral pH showed sustained release profile for all formulations. Microspheres were characterized by using advanced analytical instruments like SEM, XRD, DSC, FT-IR, Raman spectroscopy etc. Microspheres are evaluated for its swelling index, shape and entrapment efficiency. The prepared microspheres found to be stable and release controlled which consequently sustained the drug effect for longer time.

Introduction:

During the past few decades, utilization of natural polymers for the development of various drug delivery systems has been the subject of great interest. Natural gums are promising biodegradable polymeric materials. Many studies have been carried out in the fields including food technology and pharmaceuticals using gums and mucilages [1]. The traditional use of excipients in drug formulations was to act as inert vehicles to provided necessary weight, consistency and volume forthe correct administration of the active ingredient, butin modern pharmaceutical dosage forms they often fulfill multi-functional roles such as modifying release, improvement of the stability and bioavailability of the active ingredient, enhancement of patient acceptability and ensure ease of manufacture. A large number of plant-based pharmaceutical excipients are available today. Many researchers have explored the usefulness of plant-based materials as pharmaceutical excipients. Ability to produce a wide range of material based on their properties and molecular weight, natural polymers became at hrust area in majority of investigations in drug delivery systems[2]. Natural gums can also be modified to meet there quirements of drug delivery systems and thus can compete with the synthetic excipients available in the market [3]. Gums are naturally occurring components in plants,which are essentially cheap and plentiful. Natural gums are polysaccharides consisting of multiple sugar units linkedtogether to create large molecules. Gums are considered to be pathologic product formed following injury to the plant or owing to unfavorable condition such asdrought, by breakdown of cell walls (extra cellular formation, gummosis) [4]. Acacia, Tragacanth, guar gum are examples of gum [5]. They are heterogeneous in composition. Upon hydrolysis they yield simple sugar units such as arabinose, galactose, glucose, mannose, xylose oruronicacids,etc. Polymer have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically use ulin the design of modified release drug delivery systems.

Materials and Methods:

Lornoxicam obtained from C irex pharmaceuticals Ltd. Hyderabad, Other chemicals were obtained from Loba Chemie, Mumbai.

Method:

Preparation of Pellets Through Extrusion/Spheronization Process.

The powdered ingredients were passed through a 40 mesh sieve. The powders were granulated with water to get a good dough mass of extrudable consistency. The volume of the binder required was noted and thequantityof the binder used was calculated. The wet mass was extruded in to short cylinders using a cylinder roll type gravity feed extruder with a roller speed setting of 100 rpm. A granulating cylinder with 1.0 mm pore size was used and extrudates were obtained. Spheronization of the extrudates was carried out in the spheronizer using a serrated plate. The spheronization speed was varied from 300rpm to 1500rpm and spheronization time was varied from 3 min to 30 min to get pellets of good sphericity. Drying of pellets was carried out in a tray drier.

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Formulation chart of Pellets prepared through Extrusion/ spheronization Process

Formulation code	MCC %	Drug %	CMT %
F1	75	20	5
F2	70	20	10
F3	65	20	15
F4	60	20	20
F5	55	20	25
F6	50	20	30
F7	45	20	35
F8	40	20	40
F9	35	20	45

Formulation of Mucoadhesive pellets using Chitosan /Carbopol71Gcomplex through Fluid Bed Process (FBP)

Preparation of Chitosan/Carbopo lComplex

A Carbopol 71G aqueous solution (1 mg/ml) and chitosan aqueous acetic acid solution(5 mg/ml) were mixed. The resulting precipitate (carbopol/chitosan complex) was washed with distilled water and filtered under vacuum pump. The filtratewasdriedinhotairovenand thedriedcomplex wasgroundwithagrinder. The powder was passed through a 200µm sieve and used for further study

Table. 2 :Final Formulation chart of Pellets prepared through FBP

Ingredients	MP1	MP2	MP3	MP4
COMPLEX	30	30	30	30
MCC	10	20	30	40
TCP	50	40	30	20
LORNOXICAM	10	10	10	10

Preparation of mucoadhesive pellets through FBP.

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Theformulation batches were prepared using a fluid-bed processor.Thecomposition was madewith 400gof powder containing variable amounts of excipients as showed in table 11 and 12.Thesalts solutions were used as the binding-liquid with different concentrations(0.1,0.3,and0.5mol/l).Theprocessparameterswereresetas described

intable13.Another two formulations containing chitosan alone (MPC)and Carbopal alone (MPP) in ratio as MP3 formulation were also prepared.

- **Preparation of Microparticles:**

Preparation of cross-linked BFG microspheres were carried out in two stages: Firstly making an aqueous phase, secondly preparation of organic phase. This was subsequently followed by slow addition of aqueous phase into organic phase with magnetic stirring. The following step-by-step preparation is given as follows [133].

A) Aqueous Phase

Solution of BFG was prepared by dispersing (1-4% w/v) of BFG in a beaker containing 10ml of a 2M sodium hydroxide (NaOH) aqueous solution. Solution of STMP (1-4% w/v) was prepared by dissolving STMP in a beaker containing 10ml of de-ionized water. The aqueous phase was obtained by mixing the dispersed BFG solution and STMP solution and stirring the mixture for 2 min.

B) OrganicPhase

Liquid paraffin (150ml) was taken in a beaker to which 2% w/v span 80 was added and stirred at 50°C. Aqueous phase was added drop wise into the beaker under mechanical stirring (1000 rpm) to obtain the w/o emulsion. The cross-linkingreaction took place at 50°C with a constant stirring speed of 1000 rpm. After 5h of reaction,the microspheres were isolated and washed with acetone thrice. Finally, the cross- linkedBFGmicrosphereswereredriedat 40°Cfor 12handkeptinclosedcontainersfor further studies.

Characterization of polysaccharides.

Modification of polysaccharides were characterized by following methods:

Fourier Transform Infrared Radiation Measurements Compatibility of drug and excipients and modification of polysaccharides was confirmed by using a FT-IR spectrophotometer (shimadzu 8400S). The pellets were prepared by pressing the sample with potassium bromide in the ratioof1:100.The runs were made in triplicate.

Differential Scanning Calorimetry (DSC)

All dynamic DSC studies were carried out on DSC thermal analyzer 60 shimadzu.The instrument was calibrated using high purity indium metal as standard. The dynamic scans were take nin nitrogen atmosphere at the heatingrateof10°C/min.T he runs were made in triplicate.

Powder X-ray Diffraction

Powder X-ray diffraction patterns on polymers alone and their modified counterpart were obtained by using an X-ray Diffractometer (Miniflex II Desktop X-ray Diffractometer, Rigaku Corporation, Tokyo, Japan). The samples were scanned from 6° to 40° (2θ) with an increment of 0.02° and measurement time of 10 s/increment.

Swelling studies.

100mgofpolysaccharideorformulationswereplacedindistilledwaterandallowed to swell until a constant weight is attained in each medium. The microspheres were removed and blotted with

filter paper, and their changes in weight were measured.

Scanning Electron Microscopic (SEM) studies:

SEM photographs were taken with a scanning electron microscope Model Joel- LV- 5600,USA, at the required magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the pellets [138].

***Invitro* drug release studies**

The *in vitro* release of drug from the pellets was carried out in basket type dissolutiontesterUSPXXIII,TDT-08L,withautosamplercontaining900mlofpH 1.2 buffer for the first 2 hrs and in 7.4 pH phosphate buffer for the next 22 hrs. The volume of the dissolution media was maintained at 900 ml with constant stirring (100 rpm) and temperature of bath was maintained at 37 ± 0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time points and replaced with freshmedia immediately after sampling. Samples were analyzed for drug content by UV Visible spectroscopy .The release data obtained were fitted into various mathematical models to know which mathematical model is best fitting for the obtained release profile [139].

Mathematical model fitting

The release data was fitted into various mathematical models using PCP.Disso-V2.08 software to know which mathematical model will best fit the obtained release profile. The parameters like 'n' the time exponent 'k' the release rate constant and 'R' the regression co-efficient were determined to know the release mechanisms. The various models studied were

Stability Studies

Stability is defined as the ability of particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic and toxicological specification. Drug decomposition or degradation occurs during stability, because of chemical lalteration of the active ingredients or due to productin stability,loweringtheConcentration of the drug in the dosage form. The stability of pharmaceutical preparation should be evaluated by accelerated stability studies. The objective of accelerated stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature. The optimized formulations of all three dosage forms were selected for the stability studies. The accelerated stability studies was carried out according to ICH guidelines by storingthe samples at 25±2 ºC and 60±5 %RH,30±2 ºC and 65±5 % RH and 40±2 ºC and 75±5%RHfor6 months. Samples were withdrawn on 0day, 3 months, and 6 months and were analyzed for physical stability and drug content.

The drug release rates from mucoadhesive vaginal pellets were studied in 500 ml of simulated vaginal fluid pH 4.2 in type II dissolution apparatus. The temperature was maintained at 37±0.5 °Cand 50 rpm. 10 mLsample was withdrawn at hourlyinterval, filtered through a Millipore filter of 0.45 µm pore size and assayed spectrophotometrically at 271 nm for miconazole and265 nm. Immediately aftereach sample withdrawal, a similar volume of simulated vaginal fluid pH 4.2 was added to the dissolution medium [140].

Result and Discussion:

Fourier transform infrared spectroscopy (FT-IR)

Figure. 1: FT-IRspectraof lornoxicamandphysicalmixture.

The compatibility between the drug and polymer was studied by FT-IR spectra.Theposition of peak in FT-IR spectra of pure lornoxicam was compared with those in FT-IR spectra with excipients. It

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was observed that, there was no disappearance or shift inpeak position of lornoxicam in spectra of drug and excipients, which proved that drugand excipients were compatible.Hence, it can be concluded that drug can be usedwith polymer selected without causing instability in the formulation. The spectra arereportedinFigures 29[150].

DSC (DifferentialScanningCalorimetry):

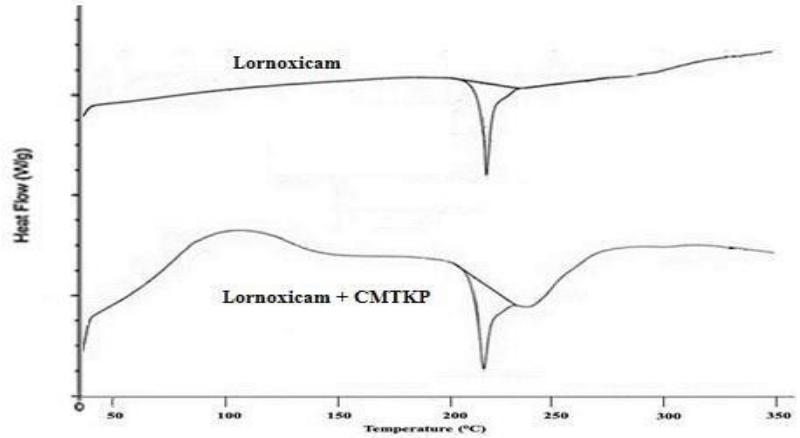
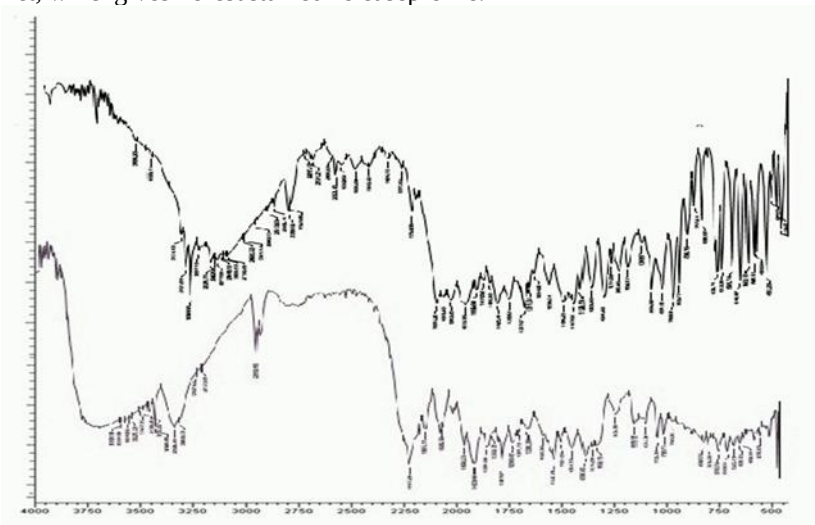


Figure. 2 :DSC thermogram of lornoxicam, lornoxicam and CMTKP

DSC studies were carried out for lornoxicam and its combination with polymers in 1:1 ratio and the thermograms obtained are presented in Figures 30. From the thermograms itwas evident that decomposition temperature oflornoxicam(218.74 °C) was not changed when a mixed with excipients (219.79 °C). Hence, itmay be inferred that there is no interaction between lornoxicam and polymers used in the preparation of pellets.

Swelling studies:

The swelling index of the TKP was found to be 18.7± 1.021 ml, and that of CMTKPwas found to be 29.23±0.63. High value of swelling index revealed the high swelling ability of CMTKP. The swelling ability of any polysaccharide depends upon its water retention capacity or water absorption capacity. As CMTKP swelling is more it increases the path length required for water to travel inside the core of pellet, whichgivesmoresustained-releaseprofile.



Conclusion:

In the present study an attempt was made in designing The dosage forms containing modified polysaccharides proved to be release modifiers in the form of sustained, mucoadhesive and colon targeted release .Further these modifications of polysaccharides can be explored in designing various drug delivery systems.

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