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DESIGN AND INVESTIGATIONS OF KETACONAZOLE MUCOADHESIVE FORMULATIONS

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ABSTRACT

For many years, the patients who are affected with acute and chronic diseases are treated with different dosage forms like tablets, pills, creams, lotions, aerosols, capsules, injection, ointments and suppositories. In the body, the concentrated drug shows less effectivity in a day when given several times for the patient. The present study was conducted is involved in the methanolic extract of the leaves like Ketaconazole and produce muco adhesive micro capsules of sodium alginate, carbopol 934 & sodium CMC to determine the physiochemical parameters and in vivo pharmacological properties.

Keywords: Ketaconazole, Microspheres, Mucoadhesion.

INTRODUCTION

For many years, the patients who are affected with acute and chronic diseases are treated with different dosage forms like tablets, pills, creams, lotions, aerosols, capsules, injection, ointments and suppositories. In the body, the concentrated drug shows less effectively in a day when given several times for the patient. The report is noticed that the drug level is fluctuated and unwanted toxicification is produced. Therefore, the interest is produced on the controlled DDS.

The variety of studies are estimated the lipid based DDS and is potential in target and controlled release of drugs. The drug consists of bio pharmaceutical components are given by pharmacosomes. The lipophilic complex is involved in the phytosomes and novel components are extracted from herbs and produce effectiveness by delivering the drug. The conventional herbal extraction with modified pharmacokinetic and pharmacological components used to treat acute diseases. The silybummarianum and ginkgo biloba and panax ginseng plants extractsphytosomes with phospholipids to produce calcium carbonate micro particles which shows effectiveness for the treatment of gastric ulcer. The present study was conducted is involved in the methanolic extract of the leaves like Ketaconazole and produce muco adhesive micro capsules of sodium alginate, carbopol 934 & sodium CMC to determine the physiochemical parameters and in vivo pharmacological properties.

EXPERIMENTAL METHODOLOGY

Chemicals and Reagents

All the polymers and reagents have been procured form SD Fine Chem Ltd, Mumbai,Quercetin was bought from Sigma Aldrich, USA. The solvents used in HPTLC were of HPLC grade and were procured from Merck Laboratories.

Preformulation studies

As part of preformulation studies the standard plot of Ketaconazole in 0.1 N HCl was drawn at concentrations 5, 10, 15, 20 and 25µg/ml spectrophotometrically (UV-Visible-1700, Shimadzu spectrophotometer) at 271 nm which resulted in a straight line with r^2 value 0.997. The FTIR analysis of the extract and the polymers had been performed to check their compatibility.

Preparation of extract loaded microspheres

Ketaconazole loaded mucoadhesive microspheres were prepared by orifice ionic gelation method with combinations of Sodium alginate, Carbopol 934 and

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Sodium CMC (carboxy methyl cellulose). Briefly weighed quantities of polymers and LME according to table 1 were dispersed in 10ml distilled water with a constant stirring at 300 rpm for 30 min. The resultant dispersion was added drop wise through a syringe (17 guage) into 10% calcium chloride solution. The so formed microspheres were kept for 30 min for complete curing and afterwards, microspheres were recovered by filtration through a sintered glass filter, dried in hot air oven at 500C for 1 hr.

Evaluation of microspheres

The evaluation of prepared microspheres was done as follows (Bhabani et al., 2009)

Percentage yield

The prepared microspheres were evaluated for percentage yield as per the equation,

% yield = Weight of microspheres recovered / Total weight (Drug + Polymer) × 100

Scanning Electron Microscopy (SEM)

To determine the surface morphology, SEM analysis was carried out using a scanning electron microscope (LEO, 435 VP, U.K.). Prior to examination, samples were mounted on an aluminium stub using a double sided adhesive tape and making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 5 kV and resolution of 4000. The cross sectioning of micro spheres was done manually using a sharp blade.

Drug entrapment efficiency (DEE)

Drug loaded microspheres (100 mg) were powdered and suspended in 100 ml dissolution medium (0.1N HCl). The resultant dispersion was kept for 24 hrs for complete mixing with continuous agitation and filtered through a 0.45 µm membrane filter. The drug content was determined using the standard graph (r^2 = 0.997). The drug entrapment efficiency (DEE) was calculated by the equation,

DEE = (Pc / Tc) × 100,

Where, Pc is practical content, Tc is the theoretical content.

Percentage moisture loss

The drug loaded microspheres was evaluated for percentage moisture loss which share an idea about its hydrophilic nature. The microspheres weighed (W_1) initially kept in desiccator containing calcium chloride at 37^0C for 24 hours. They were weighed and the process was continued till no further change in weight of sample was observed. The final weight (W_2) was noted.

Moisture loss = $[(W_1 – W_2)/ W1] \times 100$.

Determination of swelling property

Microspheres of known weight were placed in dissolution solution (0.1N HCl) for 6 hr and the swollen microspheres were collected by centrifugation and the wet weight of the swollen microspheres was determined by blotting the particles with filter paper to remove absorbed water on surface and then weighing immediately on an electronic balance. The percentage swelling of microspheres in the dissolution media was then calculated by using equation,

Sw = [(Wt- Wo)/Wo] ×100

Where, Sw= percentage swelling of microspheres, Wt = weight of the microspheres after swelling, Wo = initial weight of the microspheres.

Mucoadhesion test by falling film method

A fixed amount (N_1) of microspheres sample (approximately 100 microspheres) was added over a fresh intestinal segment of sheep, mounted on a tilted slide with an angle 45^0 and allowed to rest for 15 min. The solution was run over the segment. The effluent was collected in a Whattman filter paper and weight of detached microspheres (W_2) was noted. Percentage of mucoadhesion was calculated by using the equation

% Mucoadhesion = $W_1 – W_2/ W_1 \times 100$

Statistical analysis

All the statistical measures, Mean, Standard deviation (S.D.), Standard Error in Means (S.E.M.) and their sequential differences were calculated using one way ANOVA followed by Dunnet's T-test at level of significance P<0.001.

RESULTS AND DISCUSSION

The FTIR studies had been performed to Carbopol 934, Sodium CMC, Sodium alginate, Ketaconazoleand microspheres individually and resulted in spectra Ketaconazoleshowed peak at 3435.77 cm^{-1} corresponding to O—H stretching and all the polymers showed the peak at similar range. Interestingly, this peak is shifted to 3420.09 cm^{-1} in Ketaconazolemicrospheres suggesting the formation of hydrogen bonds between the extract and polymers. The peak at 1651.35 cm^{-1} of the extract representing the C=O functional group has been shifted to 1622.40 cm^{-1} supporting the assumption of hydrogen bonding between the oxygen atom from C=O group in extract with hydrogen atoms of OH of the polymers and vice versa. No additional peaks were seen in the spectrum of Ketaconazolemicrospheres indicating no formation of new chemical compounds which confirms that no chemical interaction had occurred.

Table 1. Formulation of Mucoadhesive microspheres

Form. no.	Sodium alginate (mg)	Carbopol 934 (mg)	Sodium CMC (mg)	% yield (X±S.D. n=3)
R1	200	50	50	74.2±0.94
R2	200	75	25	93.13±0.52
R3	200	25	75	92.76±0.687
R4	150	50	100	87.814±0.59
R5	150	100	50	85.651±0.70

Quantity of Ketaconazole added in each formulation is 400mg

Table 2. Physical parameters of prepared microspheres

Form. No.	Swelling index %(X±S.D. n=3)	Drug entrapment % (X±S.D. n=3)	Moisture loss % (X±S.D. n=3)	In vitro muco-adhesion
R1	69.34±0.48	96.359±0.21	6.5±0.12	85
R2	73.62±0.23	96.723±0.34	8.4±0.7	87
R3	70.51±0.36	97.812±0.45	5.26±0.9	90
R4	54.89± 0.52	95.436±0.82	6.10±2.3	86
R5	78.0±0.64	95.951±0.09	10.8±2.1	82

Physical Parametres

Following the table 1, five formulations had been prepared and evaluated. Prepared microspheres are subjected to the evaluation of Percentage yield, Drug entrapment, moisture loss, muco-adhesion strength, swelling index, *in vitro* drug release and *in vivo* antiulcer activity and the results were tabulated. The percentage yield of all the formulations had been evaluated and formulation R2 showed the highest percentage yield of 93% followed by R3 which is 92% also significantly similar to R2. In contrast the drug entrapment efficiency of the formulation R3 leads R2 with 97.812±0.45 And 96.723±0.34 respectively. The prepared microspheres were evaluated for particle shape and surface morphology using S.E.M. On average, each microsphere measures about 700µm in diameter. It is roughly spherical in shape and with a smooth surface. Microspheres were dried properly as evident from the absence of cracks and folds on the surface. Sectioning of microsphere showed an even distribution of drug.

The swelling indices of the formulations containing high carbopol to CMC ratio were high comparing to those with low ratio. This suggests that the carbopol is responsible for absorption water and swelling. It is clear from R5 having highest swelling index of 78% which had a high carbopol content and as suggested R3 should have the least swelling index surprisingly, R4 has swelled less may be due to the low concentration of sodium alginate. This supports the effect of sodium alginate in swelling. Moisture loss percentage values of all the formulations are under limits. Formulation R3 showed a lower value compared to all formulations. So it can be confirm that formulation is dried properly and the content of carbopol also affects the amount of moisture present in the microspheres as evident from their swelling indices. The *in vitro*muco-adhesion test was performed by falling film method. Formulation R3 showed the highest muco-adhesive strength with a value of 90, followed by R2 of 87. The least value was found with formulation R5. All the values can be inferred that muco-adhesion is affected by the presence of Sodium CMC. The higher the content of sodium CMC higher is the muco-adhesion. But, sodium alginate also possess a good muco-adhesion property which can be confirmed when formulations R1 and R5 are compared the amount of sodium CMC remained the same with varying concentration of sodium alginate which showed a better adhesion for R1. Sodium alginate is a well preferred encapsulating agent which helps sodium CMC in muco-adhesion. This suggests that the type of polymer used in the preparation of microspheres as well as their concentration influences the muco-adhesion capability. Overall, all formulations showed good muco-adhesion strength and is evident from table 2.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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