FORMULATION AND EVALUATION OF MICONAZOLE POLYMER COMPLEX SUSTAINED RELEASED DRUG DELIVERY SYSTEM

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Abstract:
Miconazole sustaimned rlrase drug delivery system can be prepared by solvent fluidized bed processor. The composition was made with 400mg of powder containing variable amounts of excipients as showed in table 1. The salts solutions were used as the binding-liquid with different concentrations (0.1,0.3,and0.5mol/l). The prepared microsphere were evaluated for FTIR, DSR, SEM, Sweling properties, micromeritic properties, drug loading and in vitro drug relases. FTIR can be concluded that drug can be used with excipients selected without causing instability in the formulation. DSC it may be confirmed that there is no interaction between miconazole nitrate and polymers used in the preparation of pellets. SEM photographs reveal the absence of drug particles on the surface of pellets showing uniform distribution of the drug in the pellet. The above results indicate the presence of complex in pellets exhibited pH independent drug release.
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.
Keywords: sustain release, Microsphere, Polysaccharide, Miconazole, FBP

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 the requirements 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 products formed following in jury to the plant or owing to unfavorable condition such a sdrought, 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, xyloseoruronic acids,etc. Polymers 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:
Miconazole obtained from Cirex pharmaceuticals Ltd. Hyderabad, Other chemicals were used in the study were obtained from Loba Chemie, Mumbai.

Method:
Preparation of mucoadhesive pellets through FBP.
The formulation batches were prepared using a fluid-bed processor. The composition was made with 400mg of powder containing variable amounts of excipients as showed in table 1. The salts solutions were used as the binding-liquid with different concentrations (0.1,0.3,and0.5mol/l). 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 [6].

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-linkedBFGmicrosphereswereDriedat 40°Cfor 12handkeptinclosedcontainersfor further studies.

Drugloadingandencapsulationefficiency

Drug loading is important with regard to release characteristics. Generally, increased drug loading leads to an acceleration of the drug release. Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the pellets.

100 mg of drug pellets were weighed and transferred to 100 ml volumetric flask containing methanol. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution is diluted to 10 ml . Percentage encapsulation efficiency is found out by calculating the amount of drug present in 100 mg of pellets. It is further calculated by using formula given inequation

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 [8].

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 [9].

Mathematicalmodelfitting

The release data was fitted into various mathematical models using 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.

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 chemicalalterationoftheactiveingredientsorduetoproductin stability,loweringthe concentrationofthedruginthedosageform.The stabilityofpharmaceutical

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 [10].

CharacterizationofChitosan-Carbopol71Gcomplex:

Fourier transform infrared spectroscopy:

The compatibility between the drug and polymer was compared by FT-IR spectra. The position of peak in FT-IR spectra of pure Miconazole nitrate was compared with those in FT-IR spectra of Miconazole nitrate with excipients. It was observed that, there was no disappearance or shift in peak position of Miconazole nitrate in any spectra of drug and excipients, which cofirms that drug and excipients were compatible. Hence, it can be concluded that drug can be used with excipients selected without causing instability in the formulation. The spectra are reported in Figures 1.

Figure 1: FT- IR Spectra of miconazole nitrate and with excipients

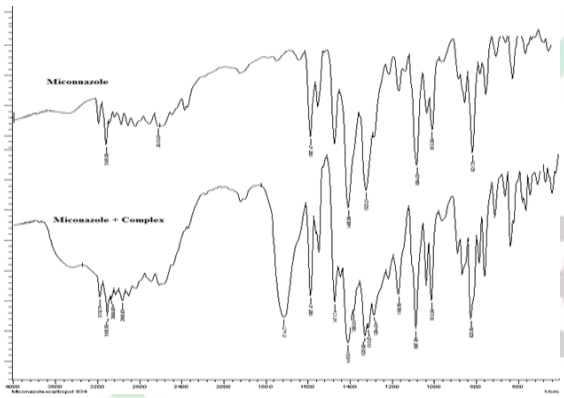


Table 2: FT-IR spectra data of Miconazole nitrate and with complex.

Group	Frequency (in cm^{-1})	
	Drug	**Formulation**
Aromatic		
C-H stretching	3181.1	3182.8
C-C stretching	1588.0	1587.4
Combination	1921.1	1920.5
Aliphatic		
C-H stretching	2826.2	2824.3
C-H bending	1474.8	1475.59
N-H stretching	3440.13	3443.15
Ether C-O-C stretching	1088.1	1086.6
NO_2 bending	1313.21	1313.57
C-Cl stretching	713.6	712.9

through FBP

Other excipients used are Talk, lactose, and tri-calcium phosphate and influence of the same on feasibility for the granulation processes was examined [176-181].

Only M4 and M7 showed a possibility to produce pellets. With the other compositions it was failed to prepare the granules, because the powder beds tended to be too sticky and became severely agglomerated. Hence it was found that Microcrystalline cellulose and tri-calcium phosphate could be the useful excipients for the pellet formation. Tri-calcium phosphate reduced remarkably the tackiness of Complex containing wet mass. Microcrystalline cellulose may also have a positive effect to achieve a suitable wet mass for pellet formation. It was also found that the both could be the additives of choice for the granulation processes.

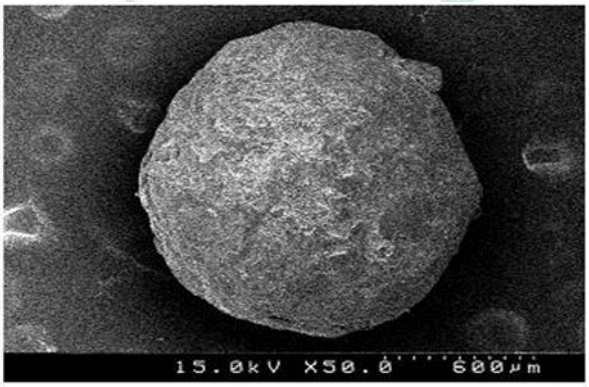
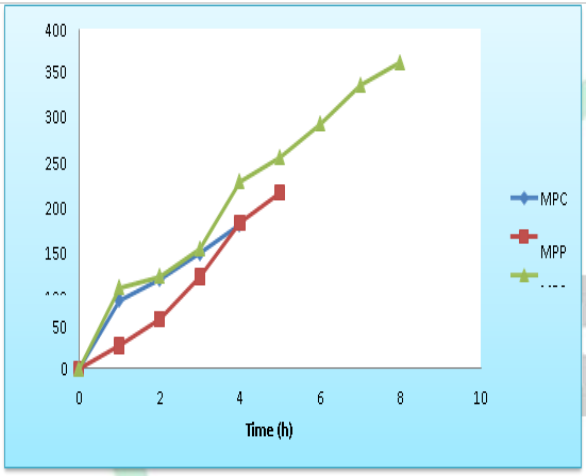


Figure 3: Scanning electron microscopy of pellet

Scanning electron microscopy (SEM) is one of the most commonly used method for characterizing drug delivery systems, owing in large part of simplicity of samples preparation and ease of operation. Scanning electron microscopy was carried out in order to characterize surface morphology, texture and porosity of the coating films. Scanning electron micrographs obtained are given in figure 51 shows the surface topography of the pellets, where a rough surface can be observed with its optimal, spherical shape. SEM photographs reveal the absence of drug particles on the surface of pellets showing uniform distribution of the drug in the pellet.

Swelling studies:

Effect of other excipients on pellet preparation



7.3 In-vitro dissolution studies

The dissolution studies were carried in USP type II dissolution apparatus using simulated vaginal fluid pH 4.5

Conclusion:

In the present study an attempt was made in designing various formulations using modified polysaccharides of natura lpolymers.The designed formulations like Sustained release pellets of CMTKP, mucoadhesive pellets of chitosan-carbopol 71gand colon targeted microparticles of STMP cross-linked BFG containing amodel drug achieved the required study objectives. 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.

All the formulated pellets were tested for their release pattern for a period of 8 hrs.

The dissolution data of the individual formulations in SVF pH 4.5 are shown in table and dissolution profiles are given in figures.

The rate of drug dissolution from chitosan pellets (MPC) was slower in SVF pH 4.5 than in pH 7. 90 % of miconazole was released in 4h. This may be due to the gel forming ability of chitosan at a low pH, which retards the rate of drug release from the pellet. In the case of MPP formulations containing carbopol, the rate of drug dissolution was

influenced by the pH of the dissolution medium. Initial burst effect was observed in pH

4.5 from carbopol pellets and entire drug was released within 5 h. This may be due to the carboxylate group of carbopol which may not dissociate at 4.5 pH resulting in less viscous gel layer around the pellet, hence rapid drug release. Complex containing formulations upon contact with simulated vaginal fluid pH 4.5 underwent swelling-driven phase transition from a glassy state to a rubbery state where molecules rapidly diffused. In these systems, the rate of miconazole release depended on the rate of gel formation around dosage form. The drug release rates were modulated by the rate of water transport and the thickness of the gel layer. The complex hydrates and this layer slowly dissolved and miconazole was released.

The rate of drug dissolution from the chitosan pellets (MPC) was faster than that from the other formulations tested in pH 7. MPC formulation released 90 % of drug in 3 h. This might be due to the inability to form gel layer around the pellet and easy disintegration characteristics of chitosan at neutral pH. In case of MPP formulation containing carbopol, the rate of drug dissolution was influenced by the pH of the dissolution medium. In pH 7, Carbopol containing carboxylic acid groups underwent ionization causing maximum swelling, resulting in fewer and smaller regions of microviscosity. The rapid gel formation acts as a barrier for the release of the miconazole, thus prolonging the drug release till 6h. Complex containing formulation MP3 upon contact with pH 4.5 underwent swelling-driven phase transition from a glassy state to a rubbery state where drug rapidly diffused. In these systems, the rate of drug release depended on the rate of

gel formation around pellet. The drug release rates were modulated by the rate of water transport and the thickness of the gel layer. The complex hydrates and this layer slowly dissolves and drug was released. Disintegration property and inability to form gel layer in neutral pH of chitosan produced initial burst effect.

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