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Research Article

EFFECT OF FORMULATION VARIABLES ON THE RELEASE BEHAVIOR OF MICROSPHERES

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ABSTRACT

The main aim of present study was to study the effect surfactant, antacid and anti adherent on the percentage drug release of antifungal agents as ketoconazole microspheres. Sustained release microspheres of ketoconazole drug were prepared using one of the best method of preparation of microspheres i.e. solvent evaporation method using cellulose derivative such as ethyl cellulose (as film forming polymer) and methyl cellulose (provides shape and integrity to the microspheres) as release rate controlling polymers. 2^2 factorial design was selected for optimization of the number of polymers to be used. Maximum percentage release of drug was seen with initial drug load of 25% w/w concentration of Ketoconazole. Approximate 70% of drug was released in acidic environment (0.1 N HCl) at 2 hours and after this it sustained and reached up to 51.22% at the end of 8 hour in Alkaline medium (phosphate buffer pH 7.2). Comparative % drug release of various variables shows significant effects as compared to drug loaded microspheres. A decline in the percentage release rate of the drug observed when mixed with antacid while increased % drug release observed when treated with surfactant. Drug release profile of anti adherent showed no change in % drug release. The release profile of Ketoconazole could be represented by Jander's equation, exhibiting pH-dependency and therefore the release of ketoconazole was governed by the diffusion within the microspheres and the solubility.

Keywords: Antifungal agents, Microspheres, surfactant, antacids, anti adherent, diffusion controlled, dissolution

INTRODUCTION

Sustained drug delivery system over the past 30 years is preferred, because the expense and complications apprehensive in promoting new drug molecules have magnified, with simultaneous recognition of the therapeutic benefits of novel drug delivery system, superior attention has been focused on development of novel controlled drug delivery system (CDDS). The main role of novel & advanced drug delivery system is to provide a stable & effective drug molecule with sub-optimal physiochemical associated / or physiological properties and develop a concrete product that may still be therapeutically effective with supplementary advantages. Oral route drug administration is the most preferable route for taking medications.[1–6]. There are various Ideal Characteristics of microspheres: [7-8] It has the capability to sustain the release rate of drug for a specified period of time. It can also act as drug reservoir having restricted particle size and its distribution of the drug in aqueous solvent for Parenteral. Microsphere considered as biocompatibility with a controllable biodegradability. There are various advantages of Microspheres[9-11] such as Size reduction which leads to increase in surface area which can enhance the solubility of the poorly soluble drug. It provides constant drug concentration in plasma which can increase patent compliance, it is having less dose and toxicity. Coating of drug with polymers helps the drug from enzymatic cleavage hence found to be best for drug delivery. The main objective was to design diffusion microsphere of ketoconazole in order to sustain the delivery of the drug and thereby reduce the gastrointestinal (GI) disturbances and adverse effects related to dose like hepatic dysfunction and allergic reactions as observed with conventional oral dosage form of ketoconazole (tablet). Microspheres of ketoconazole were prepared using dichloromethane, one of the class II solvents proposed in ICH guidelines (Q3C) to be used in the pharmaceutical industry because of their low toxic potential, as the coacervating agent to reduce residual solvent.

MATERIALS AND METHODS

Ketoconazole (KTZ) was obtained as gift sample from Q.C labs; Torrent pharmaceutical ltd. Indrad (Gujarat). Ethyl cellulose (EC) LR and methyl cellulose (MC) 4000cps were commercially obtained from S.D fine chemicals ltd; Mumbai 400030. Dichloromethane was purchased from Qualikems fine chemicals Pvt. Ltd, New Delhi. Distilled water was used throughout the study. All other materials used were of analytical grade.

Calibration Curve

Appropriate aliquots concentration from the stock solution of ketoconazole (KTZ) (100µg/ml) were used to prepare three sets of dilution consisting of different concentrations of Ketoconazole drug (KTZ) (10-60µg/ml). Aliquots of the stock solution of KTZ (100µg/ml) were taken or pipette out into a series of 10 ml volumetric flask and diluted with 0.1N Hydrochloric acid (HCl) (pH 1.26) to get final concentrations in the range of 10-60µg/ml. In a similar manner calibration curve of KTZ in alkaline phosphate buffer (pH 7.20) was prepared in the concentration range of 10-60µg/ml (Table 1). The absorbances of the resultant solutions were measured at 269.0 nm and 280.5 nm for 0.1N HCl (pH 1.26) and phosphate buffer (pH7.20) respectively.[12]

Preparation of Ketoconazole Microspheres

Ketoconazole microspheres were prepared using solvent evaporation method[13]. Ethyl cellulose (2gm) was dissolved in 20 ml of methylene chloride[14] and KTZ was added to this solution, in varying amounts, corresponding to theoretical initial loading range from 5 to 40%w/w (F1- F7). The initial loading and their corresponding formulation codes are tabulated in table 2. The polymer phase was then added to 250 ml of 0.25% w/v methylcellulose aqueous solution (overnight dispersion). Agitation was maintained at 350 rpm until complete evaporation of methylene chloride. Microspheres were then collected, washed three times with distilled water, filtered and stored under reduced pressure, overnight in a desiccator.

***In Vitro* Dissolution Study**

200 mg ketoconazole microspheres were filled in capsule were evaluated for drug release study. In vitro (dissolution) study was carried out of (F1-F5) formulations in accordance with USP modified dissolution Type I modified rotating basket apparatus using 0.1 N HCl media; 900 ml for 2 hours followed by dissolution studies in alkaline phosphate media for 6 hours at 50-55 rpm (USP NF 2004)[15]. A muslin cloth of 200 mesh size was tied over the modified rotating USP dissolution apparatus to prevent the slippage of microspheres from the modified basket apparatus[16]. 200 mg drug containing capsule was placed in the dissolution basket and 5 ml sample were taken at normal time replacing with an equal amount of fresh dissolution medium such as acidic & alkaline buffer in order to maintain the sink condition (37±0.5º C) immediately after taking of test samples. Microspheres were filtered, diluted suitably and analyzed by double beam spectrophotometer at wavelength of 269.0 nm for samples in acidic medium (0.1N HCl) and wavelength of 280.5 nm for samples in alkaline phosphate buffer media. The amount of drug dissolved in the media was calculated at various time intervals by using double beam UV spectrophotometer. The study was performed in three times to check the reproducibility for each batch and the data was plotted against time.

Effect of Formulation Variables on Drug Release from Microspheres

Effect of surfactant

The effect of surfactant on microspheres was determined by adding 0.0025%w/v of sodium lauryl sulphate in the total volume of the dissolution medium such as acidic buffer or alkaline buffer.[17] Samples were taken at regular intervals of 0.5,1,2,3,4,5,6, 7 and 8 hr and replaced with the fresh media in order to maintain the sink conditions.

Effect of antacids

The effect of antacid was studied using marketed formulation Acid- MPS on the drug release from F5 formulation.[18-19] 10 ml of the formulation was incorporated into sufficient amount of dissolution media so as to make the final volume up to 900 ml, both for 0.1 N HCl and phosphate buffer pH 7.20. The dissolution process was sampled at regular intervals and the absorbance data was recorded.

Effect of manufacturing variable

The effect of two anti adherents, talc and aerosil was evaluated on the drug release kinetics of the optimized F5 formulation. Two different batches were separately mixed with 3% by weight of talc and aerosil and dissolution studies for each batch were carried out in acidic medium (0.1 N HCl) for 2 hours followed by alkaline phosphate buffer (pH 7.2) for 6 hrs. The absorbance values of the samples withdrawn at time intervals 0.5, 1, 2, 3, 4, 5, 6, 7, 8 hours were recorded at 269.0 nm and 280.5 nm for acidic media and basic media respectively.[20]

RESULT & DISCUSSION

Calibration Curve

Calibration curve of ketoconazole was prepared in 0.1 N HCl (pH 1.26) and phosphate buffer pH 7.20 (Figure 1 & 2) in the concentration range of 10-60 µg/ml. Linear regression of the absorbance values resulted in r^2 values of 0.9995 in 0.1 N HCl and 0.9997 in phosphate buffer pH 7.20.

Preparation of Ketoconazole Microspheres

Microspheres of antifungal agent such as ketoconazole were prepared by one of the most popular techniques i.e. solvent evaporation technique with the help of mechanical stirrer as stirring devise for the preparation of microspheres. A_4 formulation was selected for initial loading range from 5 to 40 % w/w of drug and microspheres prepared were evaluated for dissolution studies.

***In Vitro* Dissolution Study**

In vitro studies were carried out in 0.1 N HCl (pH 1.26) as well as in Phosphate Buffer (pH 7.2) over a period of 8 hours resulted in drug release profile plots of % drug release vs time profile exhibited dual release behaviour of ketoconazole from microspheres (Figure 3). Initially, a rupturing effect within 2 hours was observed in formulations F4 and F5, thereafter a slow release followed till 8 hours. This dual release behaviour was not significant with formulations with low initial loadings i.e. F1- F3. This suggests drug release behavior is dependent on the concentration of the drug present in microspheres. The basic nature of the antifungal drug ketoconazole allows solubility of drug in 0.1 N HCl (acidic media) used for the test. This is supported by rapid diffusion of drug through the various dissolution media such as (acidic and alkaline media)-filled pores and channels which explains the burst effect of prominent drug release in formulation F4 and F5. Table 3 showing kinetic model treatment of various formulations F1 to F5. Slow release of drug phase indicates the higher partitioning of the drug to microsphere matrix as compared to the various dissolution conditions maintained at different buffer medium. Above point is again supported by the basic nature of drug which does not maintain its solubility in the tested alkaline medium. There are other parameters that can affect the drug release from the microspheres which include the size of the microsphere and its topography, types of polymer used and physical state of the drug molecule in the polymer phase.

Effect of Formulation Variables on Drug Release from Microsphere

Effect of surface-active agents (surfactant)

Increase in saturation solubility of the drug by solubilization in surfactant micelles could result in more rapid rate of dissolution and hence absorption. The release of poorly soluble drug from formulations may be increased by inclusion of surfactant as it tends to reduce the interfacial tension and permits the GI fluids to wet the solids more effectively. The literature has various reports on the effect of surfactant on the release of poorly soluble drugs

like drug KTZ which is insoluble in water and its absorption is dissolution rate limited inclusion of surfactant in the dissolution media should affect the quantum release of the drug. Figure 4 shows the effect of incorporation of 0.0025%w/v of sodium lauryl sulphate (SLS) in the dissolution medium when compared to the dissolution of KTZ microspheres without surfactant. As observed, the percentage of drug release in the presence of surfactant was higher amounting to 84.21% against 69.27% of drug released without the presence of SLS. An increase of 21.56% drug release was recorded in the presence of surfactant. Thus, it is suggested that SLS in suitable concentrations may be incorporated in the microsphere capsule formulation in order to enhance drug penetration and hence absorption across the GI barrier reference.

Effect of antacids

Conventional KTZ tablets are normally associated with gastric distress but concomitant administration of antacids is avoided as the drug being basic in nature dissolute more readily in acidic environment rather than the basic pH. In the present study, the formulated KTZ microspheres were evaluated for their release behaviour in the presence of antacids when compared to the release of pure drug under similar conditions. A decrease of 29.78% in terms of the drug release was observed for pure KTZ whereas a reduction of 24.97% was seen with microspheres. This reduction though not very pronounced, still supports the efficacy of the newer drug delivery system of KTZ. (Figure 5)

Effect of manufacturing variable

Anti adherents are normally incorporated into the formulation during the process of manufacturing. The anti adherents are normally hydrophobic in nature and their presence may affect the release profile of poorly soluble drugs like KTZ. In order to investigate the same, dissolution studies were carried out in the presence of talc and aerosil (3% by weight) of each. Figure 6 shows the effect of anti adherent on the release of KTZ from microspheres. The graph shows that there is no difference in the drug release from microsphere coated with talc or aerosil. Further, a paired t- test of the mean t_{50} for both talc and aerosil was computed to see if there is any significant difference in the release. The result indicated no significant difference between both variables.

Table 1: Calibration curve of Ketoconazole at different pH condition

Solvent	LOQ range (µg/ml)	r^2	Regression Equation
In 0.1 N HCl (pH 1.26)	10-60	0.9995	Y= -0.001 +0.00241X
In Phosphate Buffer (pH7.21)	10-60	0.9997	Y= 0.0011+0.00264X

Table 2: Initial drug loading and their corresponding formulation codes

Initial Loading of Drug (% w/w)	Formulation Code
5	F1
10	F2
15	F3
20	F4
25	F5
30	F6
40	F7

Table 3: Kinetic model treatment of dissolution profiles of formulations $F_1 – F_5$

Formulation	Zero order r^2	First Order r^2	Higuchi plot[21] r^2	Peppas plot[22] r^2
F1	0.8575	0.8618	0.9183	0.9045
F2	0.7904	0.7850	0.9085	0.8876
F3	0.8927	0.8783	0.8976	0.8962
F4	0.8511	0.8293	0.9116	0.9025
F5	0.8711	0.7942	0.9216	0.9134

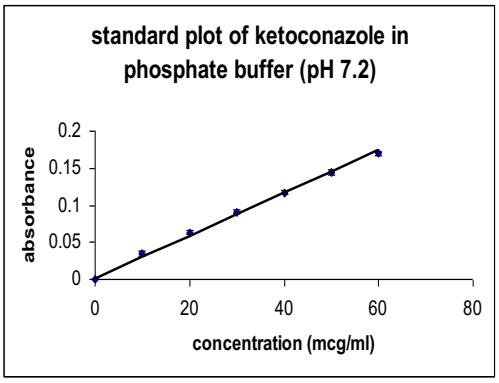

Figure 1: Standard plot of ketoconazole in 0.1N HCl (pH 1.26)

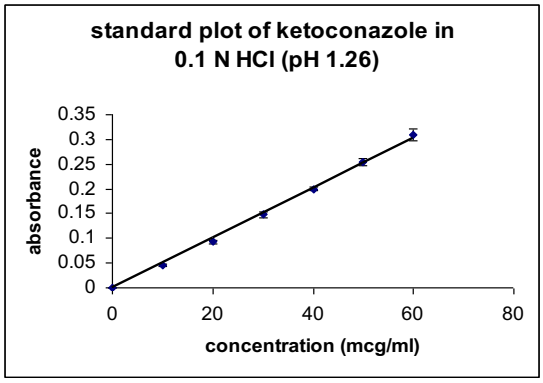

Figure 2: Standard Plot of Ketoconazole in phosphate buffer pH 7.2

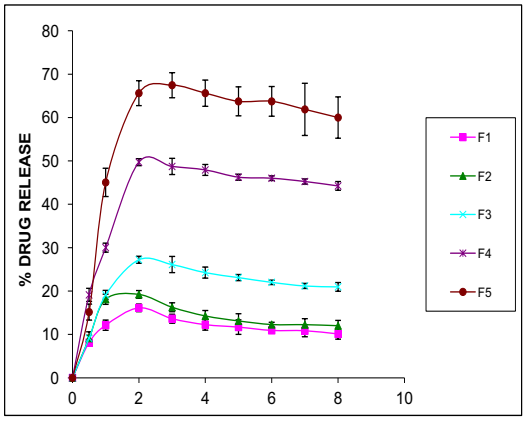

Figure 3: Comparative *in vitro* study of all the formulations of KTZ (F_1 – F_5) with respect to pure drug in 0.1 N HCl for 2 hour followed by phosphate buffer pH 7.20 for 6 hour

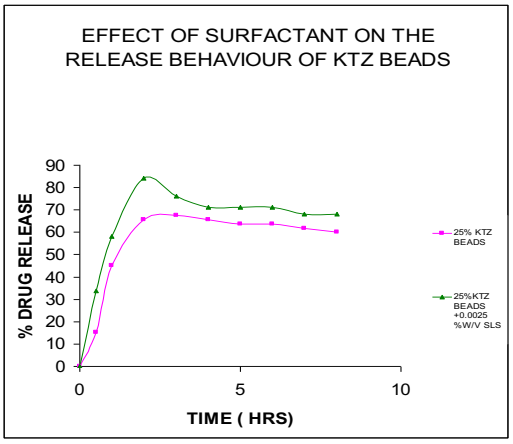

Figure 4: Effect of surfactant on the release behavior of Ketoconazole microspheres

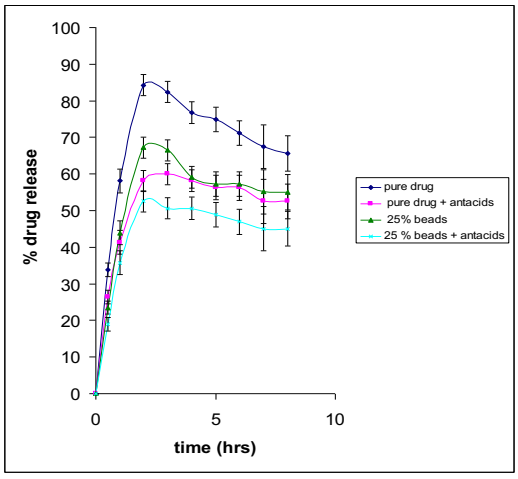

Figure 5: Effect of Antacid on the release behavior of drug release

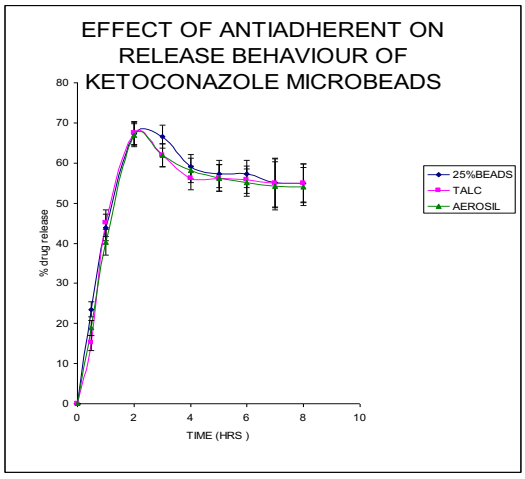

Figure 6: Effect of anti adherent on the release behavior of drug

CONCLUSION

Dissolution studies were performed using USP Basket type modified apparatus I in acidic medium (0.1N HCl) at pH 1.26 for initial period of 2 hours followed by dissolution in alkaline phosphate buffer (pH 7.20) as dissolution medium at standard temperature condition of 37°±0.5°C at 50 round per minute for the next 6 hours. Approximate 70% of drug was released in acidic medium (0.1 N HCl) at 2 hours and thereafter drug slowly controlled its release and approached nearly 51.22% at the end of 8 hour in alkaline buffer (Phosphate buffer). Various formulation variables were used to study the effect on drug release behavior. Studies revealed that variables have remarkable effect on the release behavior of the drug.

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