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Research Article

Studies in Formulation Development of Itraconazole Granules Using HPMC E 5 and HPC

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ABSTRACT
The purpose of this study was to prepare and evaluate immediate release itraconazole granules and comprehensive studies of the same. The Itraconazole granules are prepared using fluid bed processer with different concentration of HPMC E 5 (Hydroxy Propyl Methyl Cellulose) and HPC (Hydroxy Propyl Cellulose). The effect of concentration of HPMC E 5 and HPC studied using 3^2 full factorial designs. The prepared granules were physically evaluated with size, shape, surface roughness, density, moisture content, assay and drug release etc. Result shown that, both the independent variable the X_1 (concentration of HPMC E 5) is more effective than X_2 (concentration of HPC) affect on some dependent variable like size distribution, shape and surface roughness, bulk density and drug release. The optimezed batch (HPMC E 5 4 % and HPC 2 % of total weight of granules) give better quality of itraconazole granules.

Keywords: Granules, HPC, HPMC E 5, Experimental Design

INTRODUCTION

Itraconazole is an oral antifungal drug with a broad spectrum of activity belongs to Biopharmaceutical Classification Systems Class II drugs categorized with low water solubility and high permeability [1]. Itraconazole is most effective when drug concentration is maintained above the minimum effective concentration. Itraconazole is associated with several properties that formulate it difficult to formulate, such as very poor water solubility (~1 ng/mL at neutral pH) and a high log P (>5) [2]. One approach, which has been applied to producing pharmaceutically suitable dosage forms of the drug, is granulation.

Granules are agglomerates of fine powders or granules of bulk drugs and excipients with sizes ranging from about 0.1 to 2.0 mm are produced. The term "pelletization" is used synonymously with granulation, but in pharmacy this term is generally refers to the manufacture of aggregates, preferably spherical, with a narrow size distribution in the range of about 0.5 to 1.5 mm. They consist of small, free-flowing, sphere-shaped or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration [3, 4]. Granules can be manufactured by several methods. The common techniques of granulation are wet granulation, include wet massing, fluid bed granulation, spray drying, pan granulation, extrusion and palletizing and dry granulation which includes roller compaction, slugging and other granulation process includes humidification, melt pelletization etc [5-10]. The layering procedure encompass the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds [11,12]. The purpose of this study is preparing Itraconazole granules for immediate release.

MATERIALS AND METHODS

Materials

Itraconazole procured from Metrochem API Pvt. Ltd, Hyderabad, India. HPMC E 5 and HPC by Ruitai Pharmaceutical Co, China. Crospovidone, calcium carbonate, sodium lauryl sulphate were supplied by Loba Chemie. Pvt. Ltd., Mumbai. Tween - 80, diethyl Phthalate, isopropyl alcohol and dichloromethane are procured from S.D. Fine Chem. Ltd, Mumbai, India. All the reagents used in this study were of analytical grade.

Methods

Preparation of granules

The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. Itraconazole drug solution for layering is prepared by dissolving itraconazole, different concentration of HPMC E 5 and HPC, crospovidone, calcium carbonate, tween-80 and sodium lauryl sulphate in a mixture of required amount of methylene dichloride and isopropyl alcohol using mechanical stirrer. Total size 2000gm, of the batch is adjusted with adding required quantity of mannitol in the solution. Load the 700 gm sugar granules (Size 30#40 i.e. particles pass from 30 mesh and retained on 40 mesh) into the fluid bed processor (Umang Pharmatech Pvt. Ltd, Maharashtra) having 5 kg capacity. Spray the drug solution over the sugar granules with using peristaltic pump and prepare the granules at previously optimized parameters i.e at atomizing air pressure 2 bar, peristaltic pump with 2 rpm, inlet air temperature 45^0 C. After completion of drug loading dry the granules in fluid bed processor for 10 minute at 45^0 C [13].

Investigation of physicochemical compatibility of drug and excipients [14]

The physicochemical compatibility between intraconazole and excipients used in the granules was studied by using differential scanning calorimetry (DSC-Shimadzu 60 with TDA trend line software, Shimadzu Co., Kyoto, Japan). In DSC analysis, the samples were weighed (5 mg), hermetically sealed in flat bottom aluminum pans,

and heated over a temperature range of 50 to 300°C at a constant increasing rate of 10°C/min in an atmosphere of nitrogen (50 mL/min). The thermograms obtained for intraconazole, and granules were compared.

Factorial Design

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

$$Y=b_0+b_1X_1+b_2X_2\ b_{12}X_1X_2+\ b_{11}\ X_1^2+\ b_{22}X_2^2$$

where, Y is the dependent variable, b0 is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. Different concentrations of HPMC E 5 & HPC were taken for the studies. Both the variables (polymer) are taken with three different level and different batches are performed for the effect of one polymer in presence of the other polymer.

Table 1 3^2 Full Factorial Design Layout

Batch Code	Variable Levels in Coded Form		Size Distribution (% of granules between 12#20)	Shape & Surface Roughness (Grade out of 10)	Bulk Density (gm/ml)	Moisture Content (%)	Assay (%)	Drug Release at 45 min. in 0.1 N HCl pH 1.2
	X_1	X_2						
B1	−1	−1	86.14	5	1.1	1.61	22.1	98.23
B2	−1	0	88.23	5	1	1.59	22.17	98.56
B3	−1	1	89.95	6	1	1.54	22.18	98.45
B4	0	−1	94.05	9	0.8	1.5	22.12	95.23
B5	0	0	94.53	9	0.8	1.6	21.95	94.56
B6	0	1	95.21	9	0.8	1.55	22.19	91.23
B7	1	−1	95.95	9	0.8	1.54	22.19	80.12
B8	1	0	95.56	9	0.8	1.45	22.08	78.63
B9	1	1	95.82	9	0.8	1.7	22.12	76.45

Translation of Coded Levels in Actual Units

Variables Level	Low (−1)	Medium (0)	High (+1)
% of HPMC E 5 (X_1)	2	4	6
% of HPC (X_2)	2	4	6

CHARACTERIZATIONS OF GRANULES

Size

The size of granules is determined by various methods. The most ordinary and widely used method is sieve analysis. The reasons for its wide use are simplicity, lower costs, low time consumption and low turnover of operator. So, here the size distribution is performed by sieve analysis [15].

Shape and surface roughness

One of the important matters of granules preparation is to make spherical and smooth particles, suitable for subsequent successful product. Various methods can be used for measuring the shape and surface roughness of the granules. The normally used method is the analysis of microscopic or non-microscopic pictures of objects of interest. Here the shape and surface roughness is measured visually and given grade from 1 to 10 as better to best respectively [16].

Density

The density of granules can be affected by changes in the formulation and/or process, which may affects other process or factors, such as capsule filling, coating, and mixing. Variation of density from batch to batch affects the potency of the finished capsule, causes problems in batch size determination during coating and produces segregation during mixing. The density is measured by weighing accurate amount (gm) of granules, pour into measuring cylinder and measure the total volume occupied by granules [5].

Moisture content

Moisture content is generally affecting the stability of the final product. So, for most of the pharmaceutical product moisture content study is essential. Here the moisture content is measure by Karl Fischer method of determination of water content.

Table 2 Summary of Results of Regression Analysis

Coefficient	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
Size Distribution	94.54333	3.835	0.806667	-0.985	-2.655	0.08	0.997815
Surface Roughness	8.888889	1.833333	0.166667	-0.25	-1.83333	0.166667	0.992944
Bulk Density	0.788889	-0.11667	-0.01667	0.025	0.116667	0.016667	0.983173
Moisture Content	1.532222	-0.00833	0.023333	0.0575	0.021667	0.026667	0.469732
Assay	22.02667	0.298333	0.143333	-0.2325	-0.255	0.09	0.952511
Drug Release	94.09444	-10.0067	-1.24167	-0.9725	-5.26667	-0.63167	0.996701

Assay of itraconazole

Intraconazole was estimated by ultraviolet visible (UV/Vis) spectrophotometric method (Shimadzu UV-1800 UV/Vis double beam spectrophotometer, Kyoto, Japan). Solutions of intraconazole were prepared in Methanol: HCl. (99: 1). Standard solution prepared by weighing accurately about100mg of Itraconazole working standard and transfer into a 100 ml volumetric flask. Dissolve and dilute to volume with diluent, take 1 ml and put into a 50 ml volumetric flask and dilute to volume with Methanol.

Sample solution prepared by accurately weighing Itraconazole granules equivalent to 100mg of Itraconazole, put into a 100ml volumetric flask. Add approximately 50ml of the diluent, heat on water bath for 15 min. Cool and makeup with diluen and filter it. Take 1 ml of filtrate into a 50ml volumetric flask and makeup to volume with Methanol. The absorbance was measured on UV/Vis spectrophotometer at 258 nm. The method was validated for linearity, accuracy, and precision.

In vitro drug release study

The drug release study was performed using USP XXIII type II apparatus (Electrolab, TDT-06T, Mumbai, India) at 37ºC±2ºC with 100 rpm for using 900 mL of phosphate buffer (pH 1.2) as a dissolution medium. The itraconazole granules equivalent to 100 mg (454.5 mg of granules) was used for the test. Sample aliquots of 5ml were withdrawn periodically and the withdrawn samples were estimated for its drug content through UV spectroscopy. An equal quantity of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation.

RESULT AND DISCUSSION

Investigation of physicochemical compatibility of drug and excipients

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic or exothermic phase transformations). The thermograms of intraconazole (A), and granules (B), are presented in Figure 1. From the figure it was observed that there were no major changes in the melting peaks of intraconazole in the granules. This confirmed the physicochemical stability of drug with the formulation excipient used in the study.

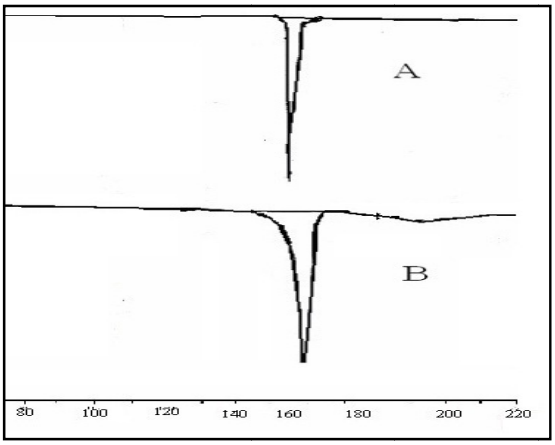

Figure 1 Investigation of physicochemical compatibility of drug and excipients

Size Distribution

The size distribution is also done by sieve analysis. The size distribution for granules varied from 86.14 % to 95.95 % in predetermined size range and showed good correlation coefficient (R^2 = 0.99). Results of the equation indicate that both the variables significantly affect the dependent variable ($p<0.05$) and X_1 (% of HPMC E 5) is more effective than X_2 (% of HPC). Moreover in both time the coefficient value is positive, so increase the concentration of polymer for 2 % to 6 % , results increased the % of granules laying in predetermined size range because of the binding property of the polymer. Size Distribution = $94.5433 + 3.835\ X_1 + 0.8066\ X_2 - 0.985\ X_1X_2 - 2.655\ X_1^2 + 0.08\ X_2^2$

Shape and Surface Roughness

The shape and surface roughness for granules varied from 5 to 9 and showed good correlation coefficient (R^2 = 0.99). Results of the equation indicate that the X_1 (% of HPMC E 5) is significantly effective than X_2 (% of HPC). So increase the concentration of X_1 from 2 % to 6%, results give good shape as well surface. Shape and Surface Roughness = $8.8888 + 13.8333\ X_1 + 0.1666\ X_2 - 0.25\ X_1X_2 - 1.833\ X_1^2 + 0.1666\ X_2^2$

Bulk Density

The density of granules can be affected by changes in the formulation and/or process, which may affects other process or factors, such as capsule filling, coating, and mixing. Variation of density from batch to batch affects the potency of the finished capsule, causes problems in batch size determination during coating and produces segregation during mixing. . The density for granules varied from 0.8 to 1.1 and showed good correlation coefficient (R^2 = 0.98). Results of the equation indicate that the X_1 (% of HPMC E 5) is significantly effective than X_2 (% of HPC). So increase the concentration of X_1 from 2 % to 6%, results, decrease bulk density because of less production of fines. Bulk Density = $0.7888 - 0.1166\ X_1 - 0.0166\ X_2 + 0.025\ X_1X_2 + 0.1166\ X_1^2 + 0.0166\ X_2^2$

Moisture content

Moisture content is generally affecting the stability of the product. So, for most of the pharmaceutical product analysis of moisture content is compulsory. Changes in the variable can not affect the moisture content. (P-value Not less than 0.05)

Assay of Itraconazole

From the result of the regration analysis it can be conclude that changing in independent variable can not affect the assay of the product. (P-value Not less than 0.05)

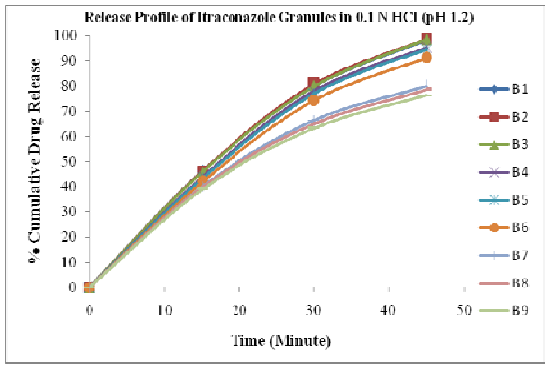

Figure 2 Release profile of Itraconazole granules in 0.1 N HCl pH 1.2

***In Vitro* Drug Release Study**

The drug release can be affected by changes in the independent variable i.e. concentration of HPMC E 5 and

HPC. The drug release of itraconazole in 45 minute varied from 76.45 % to 98.45 % and showed good correlation coefficient ($R^2 = 0.99$). Results of the equation indicate that both the variables significantly affect the dependent variable ($p<0.05$) and indicate that the X_1 (% of HPMC E 5) is more effective than X_2 (% of HPC). Moreover in both time the coefficient value is negative, so increase the concentration of polymer, results decrease in drug release. Drug release in 45 minute = $94.0944 - 10.0067\ X_1 - 1.2416\ X_2 - 0.9725\ X_1X_2 - 5.2666\ X_1^2 - 0.6316\ X_2^2$

CONCLUSION

The results of a 3^2 full factorial design reveals that the Concentrations of HPMC E 5 and HPC significantly affect the dependent variables. It could be concluded that best batch (HPMC E 5 4 % and HPC 2 %) may be may be a promising batch for good quality preparation of Itraconazole Granules. Itraconazole granules were successfully formulated as a multiparticulate system using suitable concentration of HPMC E 5 and HPC with suitable concentration of other excipients which facilitates formation granules with HPMC E 5 and HPC granules.

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