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DEVELOPMENT OF ITRACONAZOLE IMMEDIATE RELEASE PELLETS BY USING HPMC LOADED IN GELATIN CAPSULES

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ABSTRACT

The purpose of this study was to prepare and evaluate immediate release itraconazole pellets and comprehensive studies of the same. The itraconazole pellets is prepared using fluid bed processer with different concentration of HPMC (Hydroxy Propyl Methyl Cellulose). The physicochemical compatibility of the drug and the excipient studied by differential scanning calorimetry. The prepared pellets were physically evaluated with size, shape, bulk density, tapped density, compressibility index, hausners ratio, angle of repose, sieve analysis, surface roughness, density, moisture content, assay and drug release etc. The in vitro drug release profile from pellets shows that all the formulation release more than 75% drug within 90min. Optimized formulations were found to have HPMC concentration 2-5% of total weight of pellets to maximize high-quality surface, desired release, and size distribution within the range. These results indicate that pellets containing 10 % HPMC of total weight of pellets give better quality of itraconazole pellets for immediate release.

Key Words: Itraconazole, Hydroxyl propyl methyl cellulose and Immediate release.

INTRODUCTION

From time immemorial, drugs have been an inseparable part of mankind's history since they fulfill one of our most basic necessities. To administer these drugs in an appealing and palatable form and in the required amount and rate, they have to be developed into an acceptable dosage form. Thus, the concept of formulation development was evolved, resulting in solid, liquid and semi-solid dosage form (Thomas N. Tozer *et al.*, 2001)

Solid dosage forms

Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs. These have been developed into a wide range of formulations from conventional dosage forms for immediate release of the drug to controlled release dosage forms for the constant rate of drug release. Oral rouse is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost. Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. A

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simplified flow chart of the relationship of pharmaceutical dosage forms can be shown as

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action in optimum concentration, remain there for the desire time, be excluded from other site. The fact that absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage form is one of the most recent and interesting result of pharmaceutical research.

Once a day or at the most twice a day formulation is a holy grail of sorts for scientists working with oral dosage forms. A sustained release preparation that makes once or twice daily administration of drug possible might be an advantageous dosage form, especially in long-term therapy.

This ideal dosing regimen, which enhances patient compliance and helps guard against overdosing and side effects, is made possible by controlled release delivery systems, whicuse a variety of mechanisms to deliver and maintain the drug at a certain level in the patient's blood stream.

Immediate release dosage form

Conventional immediate release drug delivery system are based on single or multiple-unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat any unwanted defect or disease.

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micromeritic or macromeritic properties of materials during manufacture and/or for providing a desired drug delivery system (Bianchini R. *et al.,* 1992). The most commonly used pharmaceutical immediate release solid oral dosage forms today include tablets, capsules, granules and pellets **(**Ansel CH *et al.,* 1995).

MATERIALS AND METHOD

Materials

Itraconazole and HPMC were received as gift samples from Ra chem Ltd, Ahmedabad, India. Polyethylene glycol e20000 was a Gift sample from Clarient. Sugar spheres were a Gift sample from Shiva shakti. Dichloro methane was a Gift sample from Merck, Ethanol was a Gift sample from Merck.

Method

Preparation of ranitidine hydrochloride floating tablets

Step: 1 *Drug Loading*

Dispense all the materials as per manufacturing formulae. Shift the materials by using 50# mesh Filter the required quantity of dichloro methane and ethanol and mix it. Add hypremellose in above mixer and stir well still to get clear solution, after add itraconazole to above solution and mix it same stirring condition until get homogenous mixer. After completion of above process filter the solution by using #100 mesh. Transfer the core(sugar spheres) into the FBP and coat with the above prepared Coating solution Adjust the spray rate, inlet air temperature are in such a way that the drug coated pellets reaches a temperature of about 38^0 C-40^0 C. Over wetting of the drug coated pellets to be avoided as it may cause agglomeration. After complete quantity of the coating solution remove the pellets from FBP and kept for drying in a tray dryer. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. After checking the weight of the pellets and noting down the yield it should be packed in a double polythene bags, labeled, and securely tied. This is ready for seal coating.

Step II: *Seal Coating of Pellets*

Dispense all the materials as per manufacturing formulae. Shift the materials by using 50# mesh Filter the required quantity of dichloro methane and ethanol and mix it. Add PEG 20000 in above mixer and stir well still to get clear solution. After completion of above process filter the solution by using #100 meshes. Transfer the drug loaded pellets into the FBP and coat with the above prepared Coating solution. Adjust the spray rate, inlet air temperature are in such a way that the drug coated pellets reaches a temperature of about 38^0 C-40^0 C. Over wetting of the drug coated pellets to be avoided as it may cause agglomeration. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. After checking the weight of the pellets and noting down the yield it should be packed in a double polythene bags, labeled, and securely tied.

Preformulation Studies

Interparticulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder; such a comparison is often used as an index of the ability of the powder to flow. The bulk density and tapped density was found to be 0.248 g/ml and 0.328 g/ml respectively.

The drug and polymers were evaluated for Bulk density, Compressibility index, Hausner's ratio and Angle of repose, Melting point, Solubility. Found that all the parameters are within the official specifications.

Compatibility studies

Compatibility studies were conducted to investigate and predict physicochemical interaction between drug substance and excipients and therefore to select suitability of chemically compatible excipients. Preformulation studies are carried out with the objective of ascertaining the incompatibility of the excipients used in the existing formulation and to avoid any excipient, which is incompatible with the drug in the final formulation.

The compatibility studies were carried out at 25^0C/60% RH and 40^0C/75% RH for, 2 and 4 weeks. With respect to physical and chemical aspects, they were tested and there is no drug-excipients interactions are observed.

Compatibility studies were performed using DSC. The DSC of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the graph of each formulation correlates with the peaks of drug. This indicates that the drug was compatible with the formulation components.

Evaluation Study of Capsules

Content uniformity test

The amount of active ingredient determined by assay is within the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed with no unit outside the range of 70% to 125% of label claim. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes.

Weight variation test

Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 5 %.

Lock length **(**The United States Pharmacopeia. Twenty-third revision) It was tested by using vernier calipers.

Moisture permeation test

The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules. The degree and rate of moisture penetration is determined by packing the dosage unit together with a color revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change (indicating desiccating absorption of moisture) and comparing the pre and post weight of the packaged unit and also by the Karl Fisher titration equipment.

Disintegration

The compendial disintegration test for hard and soft capsules follows the same procedure and uses the same apparatus described later in this chapter for uncoated tablets. The capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºC and observed over the time described in the individual monograph. To fully satisfy the test the capsules disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell (Paterakis PG *et al*., 2002).

Stability Study

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH CS L6AS and IS6B.

Figure 1. DSC Graph of pure Itraconazole

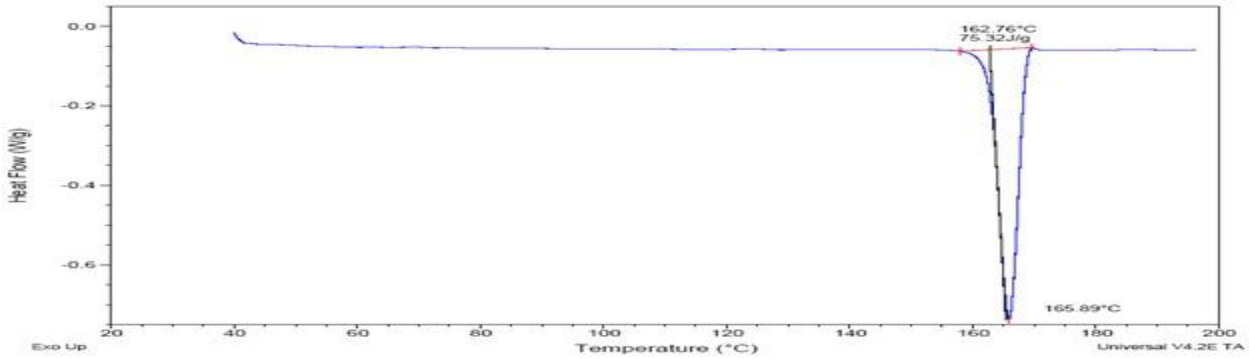

Figure 2. DSC for Itraconazole and pvpk 29/32

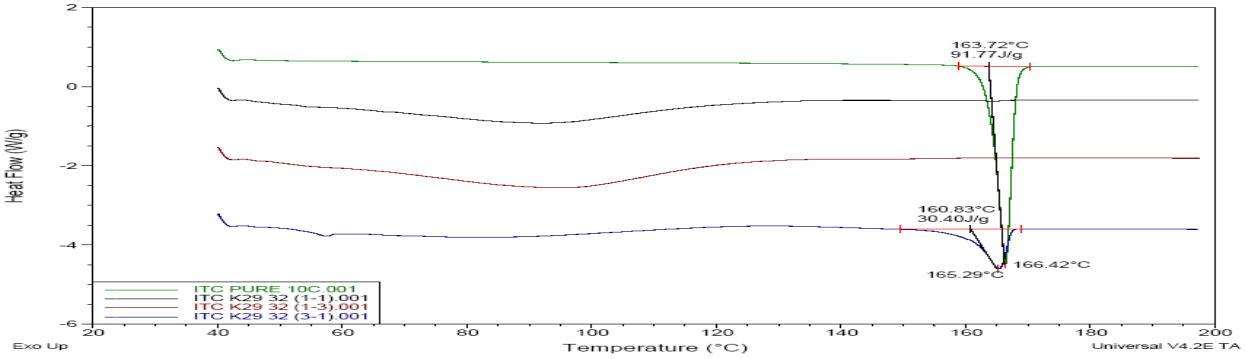

Figure 3. DSC Graph for Itraconazole and HPMC

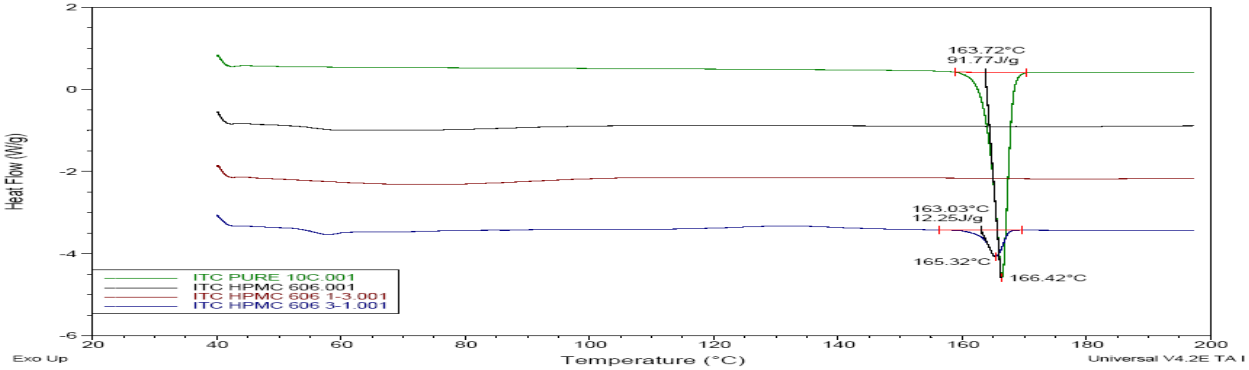

Figure 4. DSC Graph for Itrconazole and HPC

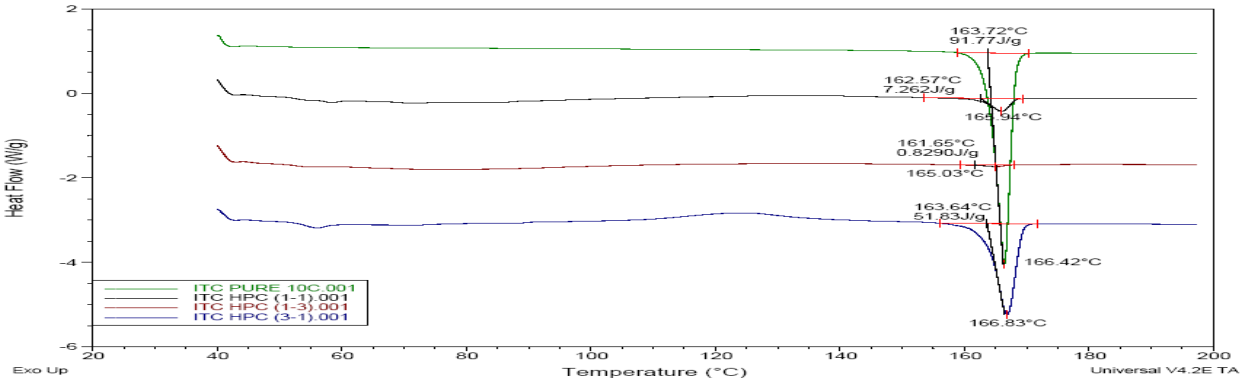

Figure 5. Release Profile of Formulated Itraconazole

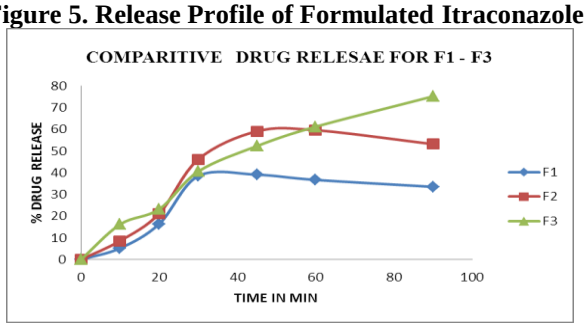

Figure 6. Release Profile of Formulated Itraconazole

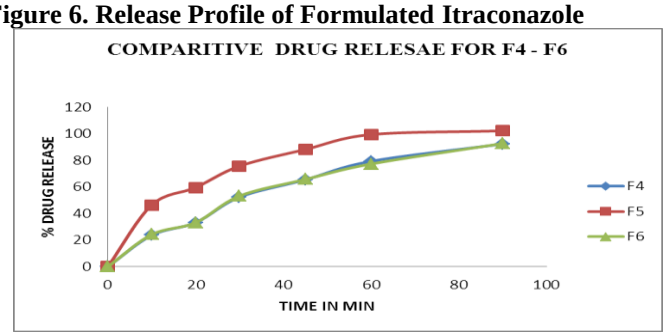

Figure 7. Release Profile of Marketed Sample Vs Formulation F4

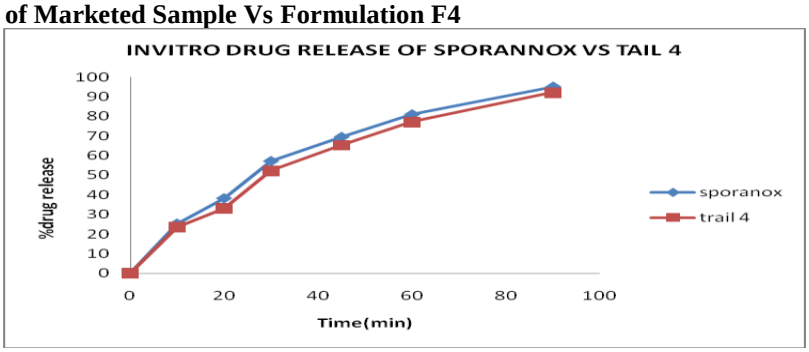

Table 1. Formula for Itraconazole 100 mg capsule

S.No	Ingredients	F1	F2	F3	F4	F5	F6
Drug Loading							
1	Itraconazole	99.82mg	99.82mg	99.82mg	99.82mg	99.82mg	99.82mg
2	Sugar Pellets (#20- #24)	239.2mg	226.5mg	203.1mg	192.0mg	182.9mg	196.5mg
3	HPMC E-5	99.82mg	120.2mg	135.9mg	150.7mg	159.3mg	153.8mg
4	Dichloro methane	45ml	45ml	45ml	45ml	45ml	45ml
5	Ethanol	30ml	30ml	30ml	30ml	30ml	30ml
Seal Coating							
6	P.E.G-20000	18.4mg	13.8mg	20.75mg	18.4mg	18.4mg	11.5mg
7	Dichloro methane	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
8	Ethanol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2. Compatibility study results

S.No	Composition details	Observation				
		Storage condition/duration				
		Initial	40 / 75 % RH		25 ± 2°C,60°C	
			2W	4W	2W	4W
1	API alone (D)	White powder	NCC	NCC	NCC	NCC
2	D+HPMC	White powder	NCC	NCC	NCC	NCC
3	D + HPC	Off white	CC	CC	CC	CC
4	D + PVPK	white powder	NCC	NCC	NCC	NCC
5	D+ SUGAR SPHERES	White powder	NCC	NCC	NCC	NCC

Table 2. Results of Compatibility Study for Itraconazole blend

Drug: Polymer	Ratios		
	1:1	1:3	3:1
ITC: PVP K29/32	Amorphous	Amorphous	Endothermic transition at 164.35°C
ITC: HPC	Endothermic transition at 165.05°C	Amorphous	Endothermic transition at 166.20°C
ITC: HPMC 606	Amorphous	Amorphous	Endothermic transitionat 164.67°C

Table 3. Physical property of Itraconazole

Bulk density(gm/ml)	Tapped Density (gm/ml)	Compressibility Index	Hausner's Ratio	Angle of repose
0.248	0.328	24.39 %	1.322	36.04^0

Evaluation of Capsules

Table 4. Weight variation of Itraconazole

S.No	Parameter	F1	F2	F3	F4	F5	F6
1	Weight variation	462.2	455.6	456.3	462.2	468.1	440.6

Table 5. Content uniformity of Itraconazole

S.No	F1	F2	F3	F4	F5	F6
Strength 460 mg	103.9%	105.7%	103.0%	102.5%	104.2%	95.7%

Table 6. Disintegration test of Itraconazole

S.No	Parameter	F1	F2	F3	F4	F5	F6
1	Disintegration time in min.	4.30	4.50	4.40	5.10	4.50	4.50

Table 7. Moisture content of Itraconazole

S.No	Parameter	F1	F2	F3	F4	F5	F6
1	Moisture content	3.2%	2.9%	3.2%	3.1%	3.3%	2.9%

Table 8. Release Profile of Formulated Itraconazole

Time (min)	Sporanox	F1	F2	F3	F4	F5	F6
0	0.00	0	0	0	0	0	0
10	25.4	5.2	8.6	16.2	23.6	46.3	24.1
20	38.3	16.4	21.2	23.2	33.1	59.5	33.1
30	57.3	38.5	46.2	40.6	52.3	75.6	53.1
45	69.6	39.1	59.1	52.3	65.3	88.1	65.6
60	81.1	36.7	59.6	61.2	79.2	99.3	77.2
90	95.20	33.5	53.2	75.2	92.2	102.1	92.6

In vitro dissolution Studies

The release rate of Ranitidine hydrochloride floating tablet was determined using INDIAN PHARMACOPEIA (IP) 96; Dissolution test apparatus (paddle method). The dissolution test was performed using 900mL of 0.1N Hcl, at 37± 0.5ºC and 75 rpm. 10ml of the solution was withdrawn from the dissolution apparatus hourly for 10 hours and the sample were replaced with fresh dissolution medium. The sample were filtered through membrane filter and diluted with suitable concentration with 0.1N Hcl. Cumulative percentage drug release was calculated using an equation obtained from standard curve.

RESULTS

Physical properties of Itraconazole blend

Physical properties of Itraconazole and polymers like bulk density, tapped density, compressibility index and Hausner's ratio and angle of repose result is shown below tab.

DISCUSSION AND CONCLUSION

The active pharmaceutical ingredient ITRACONAZOLE was subjected to Preformulation study, which encompasses the "Accelerated drug excipient compatibility study", and the results obtained with selected excipients showed good compatibility with HPMC and PVPK, but solubility of HPMC is more in selected solvents when compare with PVPK. That's why we selected HPMC for solubilizer in the formulation. The stability of the capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH and 25ºC ± 2 ºC/ 60% RH ± 5% RH, 30ºC±2ºC/65±5% RH conditions for 3 months as per ICH guidelines in HDPE containers. Finally after the duration, the product was analyzed for content uniformity, assay, and disintegration and dissolution studies. By the stability studies, the formulated Itraconazole immediate release capsules and pellets proved to be stable throughout the period of the storage. The release was found nearer in the case of pellets loaded in capsules. And dissolution profile of Itraconazole immediate release capsules were compared with that of innovator (SPORANOX). The release was found similar to that of innovator. So the prepared product was said to be equivalent with innovator. The release in the starting hours is increasing by increasing the concentration of Hpmc in the formulation F4 and it is optimized. Even though Itraconazole solution form is available in market the formulation of F4 was shows better results with innovator product and the formulation process will be easy, safe and effective.

The present study concluded that immediate release pellets in capsule of formulation F4 has relevant drug release rate rather than innovator and it has better stability, Bioavailability than the innovator.

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