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Formulation and Evaluation of Ritonavir Immediate Release Tablets by Hot Melt Extrusion Method

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ABSTRACT

In the present work, an attempt has been made to develop immediate release coated tablets of Ritonavir by hot met extrusion method using 16 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as bulk density, tapped density. The prepared IR coated tablets of ritonavir shown good post compression parameters. They passed all the quality control evaluation parameters as per USP limits. Among all the formulations, F5 formulation showed maximum % drug release i.e., 99 % in 120 mins hence it is considered as optimized formulation. The optimized formulation was compared to innovator tablets.

Keywords: Ritonavir, HPMC, Ethyl cellulose, Copovidone immediate release tablets.

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1.0. INTRODUCTION

1.1. Tablets

Tablets are defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer (simplicity & economy of preparation, stability and convenience in packing, shipping and dispensing). Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and intended method of administration (1).

1.2. Hot Melt Extrusion Method:

To date HME has emerged as a novel processing technology in developing molecular dispersions of active pharmaceutical ingredients (APIs) into various polymer or/and lipid matrices which has led this technique to demonstrate time controlled, modified, extended, and targeted drug delivery. HME has now provided opportunity for use of materials in order to mask the bitter taste of active substances. Since the industrial application of the extrusion process back in the 1930's, HME has received considerable attention from both the pharmaceutical industry and academia in a range of applications for pharmaceutical dosage forms, such as tablets, capsules, films, and implants for drug delivery via oral, transdermal, and transmucosal routes (2). This makes HME an excellent alternative to other conventionally available techniques such as roll spinning and spray drying. In addition to being a proven manufacturing process, HME meets the goal of the US Food and Drug Administration's (FDA) process analytical technology (PAT) scheme for designing, analyzing, and controlling the manufacturing process via quality control measurements during active extrusion process. In this research work extrusion technique is reviewed based on a holistic perspective of its various components, processing technologies, and the materials and novel formulation design and developments in its varied applications in oral drug delivery systems (3).

1.3. Process Technology of Hot-Melt Extrusion (HME)

Hot-melt extrusion technique was first invented for the manufacturing of lead pipes at the end of the eighteenth century. Since then, it has been used in the plastic, rubber, and food manufacturing industry to produce items ranging from pipes to sheets and bags. With the advent of high throughput screening, currently more than half of all plastic

products including bags, sheets, and pipes are manufactured my HME and therefore various polymers have been used to melt and form different shapes for a variety of industrial and domestic applications (4). The technology (HME) has proven to be a robust method of producing numerous drug delivery systems and therefore it has been found to be useful in the pharmaceutical industry as well. Extrusion is the process of pumping raw materials at elevated controlled temperature and pressure through a heated barrel into a product of uniform shape and density(5). Breitenbach first introduced the development ofmelt extrusion process in pharmaceutical manufacturing operations; however, Follonier and his coworkers first examined the hot-melt technology to manufacture sustained release polymer-based pellets of various freely soluble drugs. HME involves the compaction and conversion of blends from a powder or a granular mix into a product of uniform shape (6). During this process, polymers are melted and formed into products of different shapes and sizes such as plastic bags, sheets, and pipes by forcing polymeric components and active substances including any additives or plasticisers through an orifice ordie under controlled temperature, pressure, feeding rate, and screw speed.

However, the theoretical approach to understanding the melt extrusion process (Figure 1) can be summarized by classifying the whole procedure of HME compaction into the following:

(1) Feeding of the extruder through a hopper,

(2) Mixing, grinding, reducing the particle size, venting, and kneading,

(3) Flow through the die, and

(4) Extrusion from the die and further downstream processing.

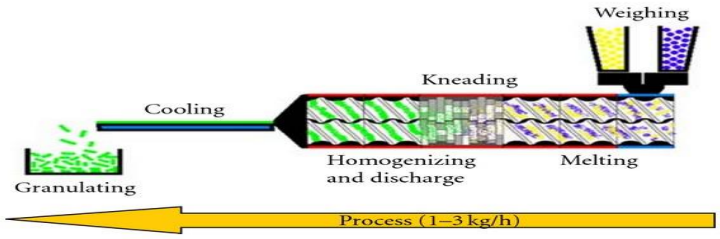

FIGURE-1 Schematic diagram of the HME process

The extruder generally consists of one or two rotating screws (either corotating or counter rotating) inside a stationary cylindrical barrel. The barrel is often manufactured in sections in order to shorten the residence time of molten materials. The sectioned parts of the barrel are then bolted or clamped together. An end-plate die is connected to the end of the barrel which is determined according to the shape of the extruded materials (7).

1.4. Single-Screw and Twin-Screw Extruder

A single-screw extruder consists of one rotating screw positioned inside a stationary barrel at the most fundamental level. In the more advanced twin-screw systems, extrusion of materials is performed by either a corotating or counterrotating screw configuration. Irrespective of type and complexity of the function and process, the extruder must be capable of rotating the screw at a selected predetermined speed while compensating for the torque and shear generated from both the material being extruded and the screws being used.(8). However, regardless of the size and type of the screw inside the stationary barrel a typical extrusion set up consists of a motor which acts as a drive unit, an extrusion barrel, a rotating screw, and an extrusion die. A central electronic control unit is connected to the extrusion unit in order to control the process parameters such as screw speed, temperature, and therefore pressure. This electronic control unit acts as a monitoring device as well (9).The typical length diameter ratios (L/D) of screws positioned inside the stationary barrel are another important characteristic to consider whether the extrusion equipment is a single-screw or twinscrew extruder. The L/D of the screw either in a single-screw extruder or a twin-screw extruder typically ranges from 20 to 40: 1 (mm). In case of the application of pilot plant extruders the diameters of the screws significantly ranges from 18 to 30 mm. In pharmaceutical scale up, the production machines are much larger with diameters typically exceeding 50– 60mm. In addition, the dimensions of a screw change over the length of the barrel. In the most advanced processing equipment for extrusion, the screws could be separated by clamps or be extended in proportion to the length of the barrel itself. A basic single-screw extruder consists of three discrete zones: feed zone, compression, and a metering zone (10).

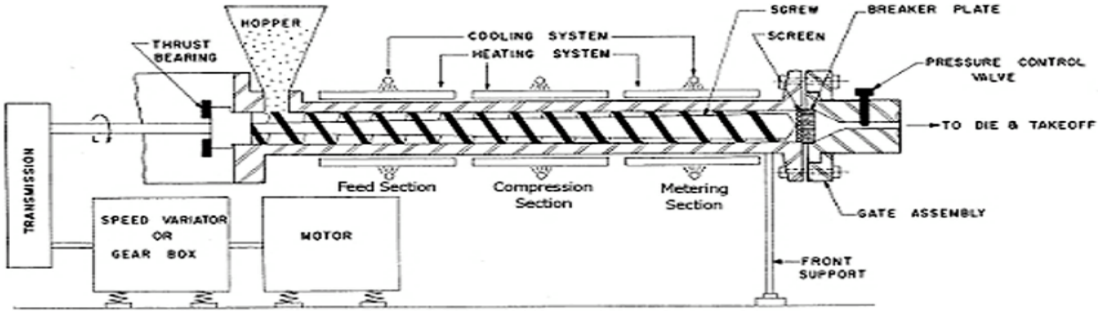

Figure 2: Schematic diagram of a single-screw extruder

Under the compression zone which is basically known as processing zone could be accompanied by few other steps such as mixing, kneading, and venting. The depth along with the pitch of the screw flights (both perpendicular and axial) differ within each zone, generating dissimilar pressures along the screw length (11).

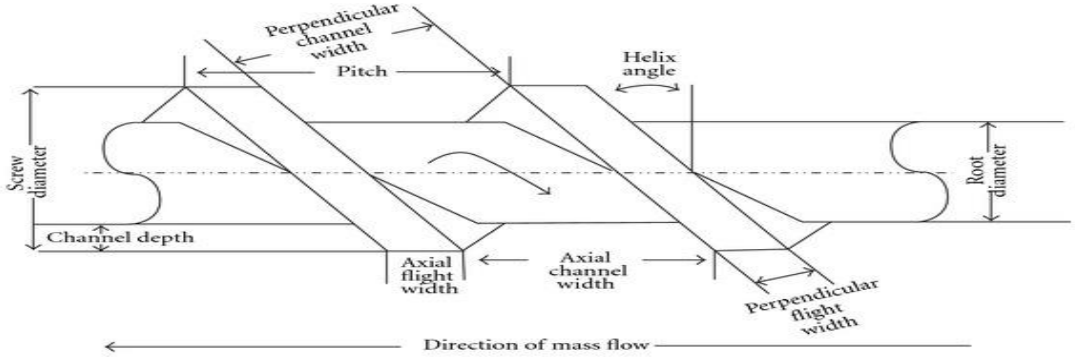

Figure 3: Screw geometry (extrusion)

Normally the pressure within the feed zone is very low in order to allow for consistent feeding from the hopper and gentle mixing of API, polymers, and other excipients and therefore the screw flight depth and pitch are kept larger than that of other zones. At this stage of the process the pressure within the extruder is very low which subsequently gets increased in the compression zone (12). This process results in a gradual increase in pressure along the length of the compression zone, which effectively imparts a high degree of mixing and compression to the material (by decreasing the screw pitch and/or the flight depth). Moreover the major aim of the compression zone is not only to homogenize but also compress the extrudate to ensure the molten material reaches the final section of the barrel (metering zone) in a form appropriate for processing. Finally the final section which is known as the metering zone stabilizes the effervescent flow of the matrix and ensures the extruded product has a uniform thickness, shape, and size (13). A constant and steady uniform screw flight depth and pitch helps to maintain continuous high pressure ensuring a uniform delivery rate of extrudates through the extrusion die and hence a uniform extruded product. In addition to the above-mentioned systems, downstream auxiliary equipment for cooling, cutting, and collecting the finished product is also typically employed. Mass flow feeders to accurately meter materials into the feed hopper pelletizers, spheronizer, roller/calendaring device in order to produce continuous films, and process analytical technology such as near infrared (NIR) and Raman, ultrasound, and DSC systems are also options. Throughout the whole process, the temperature in all zones is normally controlled by electrical heating bands and monitored by thermocouples. The single-screw extrusion system is simple and offers lots of advantages but still does not acquire the mixing capability of a twin-screw machine and therefore is not the preferred approach for the production of most pharmaceutical formulations. Moreover, a twin-screw extruder offers much greater versatility (process manipulation and optimisation) in accommodating a wider range of pharmaceutical formulations making this setup much more constructive. The rotation of the screws inside the extruder barrel may either be corotating (same direction) or counter-rotating (opposite direction), both directions being equivalent from a processing perspective

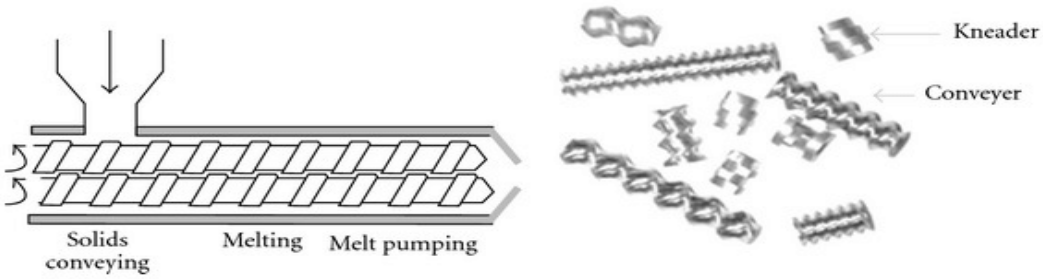

Figure 4: A twin-screw extruder and screws

A greater degree of conveying and much shorter residence times are achievable with an intermeshing setup. Furthermore, the use of reverse-conveying and forward-conveying elements, kneading blocks, and other intricate designs as a means of improving or controlling the level of mixing required can help the configuration of the screws themselves to be varied.

Ritonavir (RTV) is an antiretroviral drug and used in advance Human Immunodeficiency Virus (HIV). It is used as viral Protease Inhibitor (PI) as well as a booster for other PI drugs. It was first developed by AbbVie ltd in 1996, and is currently marketed as brand Norvir in white tablet form The British HIV association (BHIVA) guideline recommends the drug as a second line treatment for HIV, in combination with other antiretroviral drugs called Nucleoside and Nucleotide Reverse Transcriptase (NRTI). Development of viral resistance to the drug has been reported in clinical practice. Experiments have been carried out to improve the drug's efficacy

1.5.HIV life cycle:

The Human Immunodeficiency Virus (HIV) is a retrovirus, which contains a ribonucleic acid (RNA) as genetic material. It incorporates the RNA into the human DNA during its life cycle. The life cycle completes in three stages. It begins with the virus attaching and entering into the immune cell called CD4 cell. Second stage starts after entering in the CD4 cell. The virus gets uncoated and releases the genetic material into cytosol. The HIV reverse transcriptase (RT) produces viral DNA, which are transported to nucleus of the infected cell. The viral DNA is integrated to host genome by Integrase enzymes. In the third phase, the mRNA synthesises the complex of viral functional introns. They are transported out of the nucleus. Viral polypeptides called Gag and Pol are synthesized in cytosol from the introns. The viral mRNA also synthesises another polypeptide called Env in endoplasmic reticulum (ER). The Gag and Pol assemble in the cytosol and constitute viral core and reverse transcriptase of mature virus respectively. The core contains the antigenic parts such as protease (PR), integrase, RT and RNA. The Env makes up envelop of the virus. The Gag and Pol are cleaved by proteolysis process before conversion into mature functional viruses from the infected cell.

Fig 2a. Showing dimer and monomer of HIV protease. The red colour indicates water molecules. The green and purple colour represents different monomers[3].

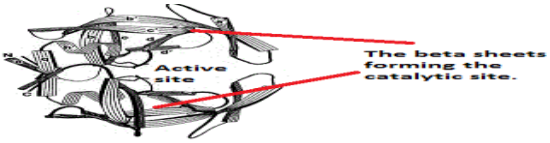

Fig 2b. HIV protease showing beta sheets and active site[3].

Figure 5. Dimer and Monomer

2.0. MATERIAL AND METHODS

2.1.1. Materials

Ritonavi, (Aurobindo Pharma Ltd) Copovidone, Sorbitan monolaurate, Dibasic calcium phosphate anhydrous, Dibasic calcium phosphate dihydrate, (Merck, India, RanQ Pharmaceuticals) Powdered cellulose, Corn starch, Mannitol, Silicified microcrystalline cellulose, Silicified microcrystalline cellulose, Microcrystalline cellulose, Sodium stearyl fumarate.

2.1.2. Film coating material

Aquarius prime BAP 118010 white IH, Purified water USP (solid content 15 % w/w)

Procedure

Preparation of Ritonavir Immediate Release Tablets:

Wet granulation

Sifting

Sift the ritonavir USP (micronized) through ASTM ≠ 20 mesh

1. Sift copovidone through ASTM ≠ 40 mesh.
2. Heat the sorbitan monolaurate to 60-70° C or till it forms a clear transparent solution into a stainless steel container.
3. Ingredients of step 1 were loaded into 3 ltr Rapid Mixer Granulator (RMG) and spray sorbitan mono laurate of step 3 slowly on this material with impellar at fast speed and chopper at slow speed then continue the mixing for 2 minutes after the complete spraying of sorbitan monolaurate with impellar at fast speed and chopper at slow speed.
4. Unload the material of step 4 with impeller at slow speed and check the weight of the material.
5. Calculate and weigh the actual quantity of material office step 5 required for the required for the batch.
6. Load about 25 % w/w of sifted copovidone of step 2, material of step 6 and about 25% w/w of sifted copovidone of step 2 into Rapid mixer granulator and mix for 5 minutes with impeller at slow speed.
7. Add the remaining quantity of sifted copovidone of step 2 to the material of step 7 and mix for 5 minutes with impeller at slow speed.
8. Unload the material of step 8 with impeller at slow speed.
9. Load the material of step 9 into a feeding Hopper of hot melt extruder and start the melt extrusion process.
10. Record the actual parameters observed
11. Collect and mill the extrudes of step 10 in Multi Mill through 0.5 mm screen at fast speed with knives forward direction and collect the past extrudes.
12. Weigh the milled extrudes of steps for 12 based on the yield of mild extrudes of step 12 calculate the quantities of the dibasic calcium phosphate, anhydrous dibasic calcium phosphate dehydrate, powdered cellulose, corn starch 400l mannitol, silicified microcrystalline cellulose (Prosolve SMCC® 90), silicified microcrystalline cellulose(Prosolv SMCC® 50), microcrystalline cellulose and sift together through 40 ASTM mesh
13. Calculate the required quantity of sodium stearyl fumarate based on the end of milled extrudes of step 12 where the quantity of sodium stearyl fumarate and sift through ASTM ≠ 60 mesh
14. Load the mild extrudes of step 12 and shifted material of a step 13 into a low shear blender and blend for 25 minutes
15. Add the sifted sodium lauryl stearyl fumarate of a step 14 to the material of step 15 and blend for 5 minutes and unload.
16. Compress the blend of step 16.
17. Prepare coating suspension by dispersing Aquarius prime 118010 white in specified amount of purified water to achieve 15% w/w solid content using suitable stirrer. Stir the suspension for about 45 minutes
18. Load the core tablets of step 17 in the coating pan and pre warm the tablets at an inlet air temperature of 50 ± 10°C with an intermittent inching of the coating pan.

19. Start the spray of coating suspension of step 18 after the product temperature reaches 35 ± 5°C, continue the coating till a coat weight build up of 2.08% w/w ± 0.50°C w/w per tablet was obtained.

2.1.3. Different composition of ritonavir immediate release tablets (14).

TABLE-1 Formulation of ritonavir immediate release tablets

Trial No.		**F1**	**F2**	**F3**	**F4**	**F5**
S.No	**Ingredients**	**Qty per unit (mg)**				
Intragranular (Hot melt extrusion)						
1.	Ritonavir USP(micronized)	100.00	100.00	100.00	100.00	100.00
2.	Copovidone USNF	581.20	581.20	531.20	481.20	481.20
3.	Sorbitan monolaurate USNF	0.00	6.80	3.4	6.80	0.00
4.	Dibasic calcium phosphate anhydrous USP	70.00	70.00	70.00	70.00	70.00
5.	Dibasic calcium phosphate dihydrate USP	50.00	50.00	50.00	50.00	50.00
6.	Powdered cellulose	85.00	85.00	85.00	85.00	85.00
7.	Corn starch USNF	93.00	93.00	93.00	93.00	93.00
8.	Mannitol USP	85.00	85.00	85.00	85.00	85.00
9	Silicified microcrystalline cellulose (Prosolve SMCC®90) IH	44.00	44.00	44.00	44.00	44.00
10	Silicified microcrystalline cellulose (Prosolve SMCC®50) IH	18.00	18.00	18.00	18.00	18.00
11	Microcrystalline cellulose USNF	114.60	114.60	114.60	114.60	114.60
12	Sodium stearyl fumarate USNF	2.40	2.40	2.40	2.40	2.40
Core Tablet weight		**1243.20**	**1250.00**	**1196.00**	**1150.00**	**1143.20**
Film coating material						
13	Aquarius prime BAP 118010 white IH	35.72	35.72	35.72	35.72	35.72
14	Purified water USP (solid content 15 % w/w)	q.s	q.s	q.s	q.s	q.s
Total tablet weight		**1268.20**	**1275.00**	**1221.60**	**1175.00**	**1168.20**

2.2 EVALUATION OF TABLETS

2.2.1. Weight Variation Test:

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100 / W_A$$

As the total tablet weight was 655 mg, according to USP, out of twenty tablets ±5 % variation can be allowed for not more than two tablets.

2.2.2. Hardness Test:

10 tablets from each batch were selected and hardness was measured using tablet hardness tester to find the average tablet hardness or crushing strength. Hardness of 4 kg is considered suitable for handling the tablets.

2.2.3. Tablet Thickness:

Thickness and diameter of formulation trials were measured using a Digital vernier Caliper, Thickness Gauge. 10 tablets of each trial formulation were taken and measured individually at frequent intervals.

2.2.4. Friability (%):(15).

Friability was determined by taking 20 tablets. Tablets samples were weighed accurately and placed in Friabilator after the given specification 100 revolutions per min (4 min at 25 rpm). The tablets were weighed again and % friability was then calculated by:

$$\%F = \frac{W - W_0}{W} \times 100$$

Where, % F = Friability of tablets in percent.
W = Initial Wight of tablets.
W_0 = Final weight of tablets.

2.2.5. Comparison of Dissolution Profiles:

According to US FDA guidance for dissolution data equivalence, model independent approach is recommended. This involves the use of similarity (f_2) and dissimilar factor (f_1) which provides simple means to compare the dissolution data.

2.2.6. Similarity factor (f_2): (16).

The similarity factor f_2 was defined as a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. This was calculated to compare the test product and reference product with

respect to the drug release or dissolution profiles(17). It was calculated data according to the following equation:

$$f_2 = 50 \times \log \{[1+ (1/n) \sum t=1\ n\ (Rt - Tt)2]^{-0.5} \times 100\}$$

Where, n = number of full time points

Rt = the reference profile at the time point t

Tt = the test profile at the same point t

2.2.7. Dissimilarity factor (f_1): (18).

It is also called as Difference factor. It describes the relative percentage error between two dissolution profiles. The percent error is zero when the test and reference profiles are identical and increases the proportionality with the dissimilarity between the two profiles.

$$f_1 = \{[\sum t=1\ n\ (Rt-Tt)] / \sum t=1\ n\ Rt]\} \times 100$$

2.2.8. Assay: (By HPLC)

2.2.9. Instrumentation:

a. High performance liquid chromatography system with Waters 2695 separations module/Waters E2695 separations module with 2489 UV- Visible detector

b. Data handling system (Empower pro).

c. Analytical column: A stainless steel column 250 mm long, 4.6 mm internal diameter filled with Octyl silane chemically bonded to porous silica particles to 5µm diameter.

[Use Kromasil- 100 C_8 5µ (250 x 4.6mm)] or Equivalent.

3.0. RESULTS AND DISCUSSION

The present study was undertaken to formulate ritonavir IR tablets. The study involves preformulation studies of drug and excipients, formulation and processing development along with evaluation of tablets made with the optimized formulation. Finally film coated tablets were evaluated by *in vitro* methods

3.1. Physical Characterization of Active Pharmaceutical Ingredient (API)

Table 2: *Physical characterization of API*

S.No:	Description	Result
1.	Appearance	White crystalline tan powder
2.	Solubility	insoluble in water
3.	Moisture Content	2.0% L max

3.2. Solubility Studies

The solubility of ritonavir drug was studied in six different media. The API was found to be insoluble in water and also freely soluble in all the following medias.

Table 3: *Solubility Studies of ritonavir in various solvents*

Solvent	pH(Approx)	Solubility(mg/ml)
0.1N HCl	1.2	171.44
0.01N HCl	2.1	132.01
Acetate buffer pH 4.5	4.5	48.45
Purified water	6.5	198.26
Phosphate buffer pH 6.8	6.8	132.45
Phosphate buffer pH 7.2	7.2	114.33

3.3. Flow Properties

Bulk density, tapped density, carr's index and Hausner's ratio were calculated for checking the flow property of the API. The results of the tests are shown in the table which indicates that the API exhibit very poor flow as its nature is very fluffy.

Table 4: Flow properties of API shown in the table

S. No	Flow properties	Result
1	Bulk density (g/ml)	0.136 ± 0.30
2	Tapped density (g/ml)	0.253 ± 0.29
3	Carr's index (%)	46.26 ± 2
4	Hausner's ratio	1.861 ± 0.06

Table 5: *Drug Excipients physical compatibility studies*

S.No	Ritonavir +excipients	Ratio	Initial Observation	Observation after 1month		
				40°C/75%RH (open)	40°C/75%RH (closed)	2 – 8°C closed
1.	Ritonavir	N/A	White color	No change in color	No change in color	No change in color
2.	Ritonavir + MCC	1 : 1	White color	No change in color	No change in color	No change in color
3.	Ritonavir + Lactose monohydrate	1 : 1	White color	No change in color	No change in color	No change in color
4.	Ritonavir + HPMC	1 : 1	White color	No change in color	No change in color	No change in color
5.	Ritonavir + Ethyl Cellulose	1 : 1	White color	No change in color	No change in color	No change in color
6.	Ritonavir + Aerosil	1 : 1	White color	No change in color	No change in color	No change in color
7.	Ritonavir + Magnesium stearate	1 : 1	White color	No change in color	No change in color	No change in color

3.4.Precompression Studies

Bulk density, tapped density, compressibility index and hausner's ratio test was performed. The prepared blends of various formulations showed bulk density in the range of 0.30 to 0.51, which indicates the flow of blends are fair to good; tapped density in the range of 0.42 to 0.71 g/ml respectively, which indicates that there is good flow. The % compressibility index range was found to be 24 to 33%, which indicates the flow is poor and passable of the blends and Hausner's ratio in the range of 1.32 to 1.50, Hausner's ratio indicates the flow is poor.

3.5.The limits of the entire test indicate that the blend flow was poor.

Table 6 Precompression data

S.No	Formula	Bulk density(g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
1	F1	0.595	0.735	19.05	1.235
2	F2	0.581	0.757	23.27	1.303
3	F3	0.581	0.735	20.93	1.265
4	F4	0.581	0.781	25.58	1.344
5	F5	0.555	0.735	24.44	1.323

3.6. Post compression Studies

Ten tablets of each formulation (core and coated) are selected randomly and average weight was determined. Then individual tablet is weighed and compared with an average weight. The USP limit of % allowed variation of tablets above 400mg is ± 5%. The % weight variations of the formulations mentioned in above table are within the limit.

The values mentioned in above table for hardness test are within the limit and matching the innovator products Thickness of all the formulations was found in the range for core tablets 5.75 to 6.06 mm. and coated tablets for 6.09-6.67 Friability is the ability to withstand the abrasion during transporting. The friability limit according to USP is 0.5 to 1 %. The values mentioned for all the tests are within the limit.

Table 7*:* Evaluation parameters of core tablets are shown in the table

S.No	Formula	Thickness (mm) Avg of 10 tablets	Hardness (KP) Avg of 10 tablets	Friability (%w/w)
1.	F1	7.83-7.91	22.2-26.5	Nil
2.	F2	7.82-7.91	22.7-26.9	Nil
3.	F3	7.53-7.67	21.5-26.5	Nil
4.	F4	7.18-7.25	23.5-27.8	Nil
5.	F5	7.09-7.22	23.3-27.2	Nil

3.7. DISSOLUTION STUDIES

The dissolution was carried out for different formulation trials and also for the innovator. The various results that are obtained are tabulated below.

Table 8: In vitro drug release data of innovator

Time (mins)	% Drug Release
10	42.49±0.62
20	60.98±0.78
30	71.29±0.98
45	78.12±0.79
60	83.62±0.21
90	87.21±0.74
120	91.22±1.09

Table 9: Comparison of Drug release of Reference, Formulation 5 and Stability loaded Formulation 5

Time (mins)	% Drug Release (innovator)	F1	F2	F3	F4	F5
10	14	15	14	20	19	**24**
20	35	34	32	42	39	**45**
30	52	51	49	60	58	**65**
45	72	71	69	81	81	**83**
60	86	85	85	92	91	**93**
90	94	98	99	97	100	**99**

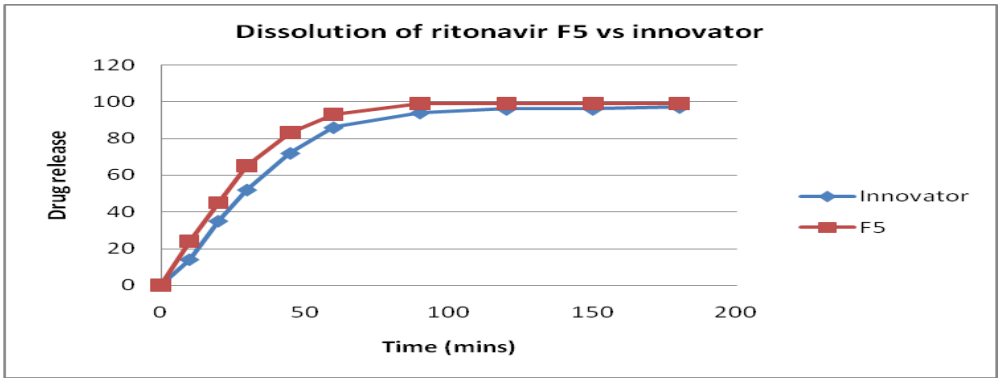

Figure 6: Comparison of Dissolution profile of ritonavir formulations Vs Innovator

3.8. Stability Data of formulation F5

Dissolution of trial F-5 tablets was comparable with marketed product. So tablets of this batch were kept for stability studies. The results of stability studies are shown in Table after 3 months the physical parameters of the tablets were same. Water content and related substance are within limits. The tablets were tested for Physical appearance, assay, relative substances, dissolution, moisture content at initial, 1st month, 2nd month and 3rd month in accelerated conditions (40±2⁰C & 75±5%RH).

Table 10. Stability study data (accelerated) of Formulation – 5:

S.no	Parameters		Specifications	Test Condition (Accelerated)			
				40 ± 2⁰C & 75 ± 5% RH			
				0 Day	1M Month	2M month	3M Month
1	Description		Immediate release coated tablet.	Comply	Comply	Comply	Comply
2	Moisture content		Not more than 2.0%	1.427%	1.326%	1.211%	1.143
3	Assay		NLS 90% &NMT 110%of labeled amount of drug.	100.9%	99.2%	99.3%	99.5%
4	Related substances by HPLC	Impurity A&B	NMT 0.5%	0.02	0.04	0.03	0.04
		Impurity a,b,c,d	NMT 2.3%	0.60	0.69%	0.058%	0.68%
		unidentified impurity	NMT 0.13%	0.06%	0.08%	0.09%	0.10%
		Total impurity	NMT 1.6%	1.01	1.25	1.39	1.55

Stability studies for the optimized tablets were carried out at a temperature and relative humidity of 40ºC/ 75% ± 5% RH for a period of three months. Tablets are evaluated for physical appearance, color, moisture content, assay, related substances and dissolution studies. An average drug content of the tablets 97.625% w/w. Tablets have not shown any significant change during storage. Hence, it was concluded that the optimized tablets have good stability during their shelf life.

Formulation -5 Stability sample withdrawn 40⁰C/75%RH three months % drug releasing time profile comparing initial product with marketed product.

Table 11: Stability sample with drawl 40⁰C/75%RH three months % drug releasing time profile

S.no	Time (min)	Marketed product% drug release	Initial for formulation-5 %drug release	40⁰C/75%RH(F5) % drug release
1	0	0	0	0
2	10	10.08 ± 2.02	9 ± 2	9 ± 3
3	20	22.21 ± 4.0	22 ± 2	22 ± 4
4	30	42.30 ± 2.0	42 ± 2	42 ± 2
5	45	55.40 ± 2.45	57 ± 1	56 ± 3
6	60	75.32 ± 3.0	72 ± 3	72 ± 2
7	90	89.65 ± 2.02	87 ± 2	86 ± 5
8	120	96.32 ± 2.0	92 ± 2	91 ± 4
9	150	98.32 ± 1.5	96 ± 1	95 ± 2
10	180	99.01 ± 4.0	98 ± 5	97 ± 6

4.0. CONCLUSION

The present work was carried out to formulate and evaluate Ritonavir immediate release tablets.The drug excipient compatibility studies were carried out by HPLC. Based on the results, it was confirmed that there is no interaction between drug and excipient at different conditions. Eight formulation trails of Ritonavir tablets were conducted using different polymers at different concentrations. Physical characterizations of marketed product API and solubility studies Flow properties of API were studied and it was confirmed that Ritonavir exhibits very poor flow properties Blends of all formulations were prepared and pre compression properties were studied. The results indicated that all the formulation blends exhibited good flow properties, Formulations were compressed by hot melt extrusion method and subjected to post compression studies. For core tablets and coated tablets respectively. The results were found to be within the limits.

In vitro drug release of all formulations was carried out in dissolution medium 900 ml purified water and in multimedia buffer by using USP type – II (paddle). Figure 6 showing dissolution profile of different formulations of ritonavir immediate release tablets. Among formulations developed by wet granulation method F5 shows highest % drug release (99 %) at 120 mins The optimized formulation was subjected to accelerated stability studies at a temperature and relative humidity of 40̊ C/ 75% ± 5% RH for a period of three months. Tablets are evaluated for physical appearance, color, moisture content, assay, related substances and dissolution studies.

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