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A NOVEL APPROACH FOR FORMULATION OF ITOPRIDE HCL MUPS SUSTAINED RELEASE TABLET

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ABSTRACT

MUPS tablet was prepared to control the release of Itopride Hydrochloride over a prolong period of time as multi unit particulate system are familiar, proven, easy to formulate and economical. The sustained released pellets containing Itopride Hydrochloride were prepared using a Fluidized bed processor technique. Amount of Microcrystalline cellulose (Avicel pH102, Hypromellose 15 cps and Ethyl cellulose 50 cps were taken as the formulation variables for optimizing to keep round shape of pellets and percentage release of drug. The pellets were evaluated for Physical characterization, Assay, Sizing, Aspect ratio, density, SEM, In-vitro drug release and Binder's concentration tends to very effective pellets shape and size. Percentage release of drug intended to very non-linear with polymer type and percentage of coating on the pellets. In present investigation attempts were made to prepare 8 batches of multi unit particular tablets of Itopride Hydrochloride by using different polymers namely ethyl cellulose 50 cps and HPMC E-6 cps. The prepared tablets were evaluated for weight variation**,** thickness, percentage drug content, content uniformity, hardness disintegration time, *in* vitro drug release.

Keywords: Itopride Hydrochloride, MUPS, Aspect Ratio, SEM

INTRODUCTION

Itopride, a novel prokinetic agent is unique and different from the available prokinetics because of its dual mode of action and lack of significant drug interaction potential. Itopride is a newly developed prokinetic agent, which enhances gastric motility through both antidopaminergic and anti-acetylcholinesterasic actions.[1] Thus a prokinetic drug like Itopride, by virtue of its efficacy and tolerability could be considered as a drug of first choice and a welcome addition to the drug armamentarium for the symptomtomatic treatment of NUD and other gastric motility disorders including functional bowel disorders. Itopride is one of the best molecules for treatment of GERD. Itopride is used in the treatment of gastrointestinal symptoms caused by reduced gastrointestinal motility, like feeling of gastric fullness, upper abdominal pain, anorexia, heartburn, nausea and vomiting; non-ulcer dyspepsia or chronic gastritis.[2] Itopride hydrochloride, a novel prokinetic agent is best candidate for GERD. Itopride 150 mg can be given once in a day given along with Proton pump inhibitor[3]. By developing the sustain release MUPS formulation of Itopride hydrochloride, the frequency of both drug can be reduce to once only to obtain good therapeutic response. The prepared formulation is usually taken on an empty stomach about an hour before meals and efficient to overcome GERD for 24 hr. Special formulation for Itopride hydrochloride is required is Pellets, which gives more stability to Itopride hydrochloride from compression and other stress condition during formulation and storage conditions. And also Pellets offers some additional advantages like, disperse freely in GI tract, maximize drug absorption, and minimize local irritation of the drug which indicates pellets can be used for sustain drug delivery[4]. With regard to the final dosage form, the multiparticulates can be filled into hard gelatin capsules or be compressed into tablets. The compression of multiparticulates into tablets is becoming more popular, especially in the USA, where hard gelatine capsules have been tampered. So, this study focused

on the development of sustains release tablets containing pellets. To develop a stable formulation of Itopride hydrochloride MUPS Pellets with optimization of polymer, in different concentration, for matrix former on pellets and to develop a tablet formulation for Itopride hydrochloride Pellets with optimization of different diluents and different disintegrating agents with different Concentrations[5].

MATERIALS AND METHODS

Itopride Hydrochloride was obtain as a gift sample from MSN Pharmachem Pvt., Hypromellose 2910 (6 cps), Hypromellose 2910 (15 cps) from S.D Fine chem., Ethylcellulose from Roquette Pharma, Aerosil and Crosspovidone from S.D Fine chem., Polysorbate 20 from BASF Ltd, Magnesium stearate from Signet chemicals, Celesphere 203 and Lake Sunset red from S.D Fine chem., IPA from Triveni Chemicals

Method for Preparation of MUPS Tablet:
Different batches of Itopride Hydrochloride were prepared by using different polymer namely Hypromellose 2910 (6 cps), Hypromellose 2910 (15 cps), Ethyl cellulose. The process included three steps are as under.
1. Drug loading 2. Polymer coating 3. Compression

Step I: Drug Loading
Composition for drug coating on pellets:
For drug coating, drug Itopride Hydrochloride along with Binder Hypromellose were taken. Here binder concentration had been taken from 2% to 6% because Hypromellose has been used as binder for in this range of concentration. Here binder was used because of drug particles can stick to the pellets and make a uniform drug coating on pellets and appropriate amount of drug to be contained in to selected quantity of pellets. Here Talc is used as dispersing agent in 2-5%.

Preparation of drug coating suspension:
Weigh all ingredients & prepare binder solution. Took 100 gm IPA and 50 gm purified water in container (250 ml) & kept it under stirring add Itopride Hydrochloride to the vortex of the solution under stirring &stir for 20 min. Took 110 gm of water in container (250 ml) Add HPMC E- 6, Mag. Carbonate, starch, Sugar & Talc init under stirring & stir it for 20 min, Mix the dispersion of above solution well under stirring Rinse the container which remaining 60 gm of IPA(isopropyl alcohol) & stir it final solution for 15 min then Pass the dispersion using Nylon cloth of mesh No.200 now the solution is ready for Drug loading. Then drug loading using the dispersion over Celesphere 203 in the chamber of the FBP.

Procedure:
Itopride Hydrochloride drug solution was prepared and sprayed on spheres using a fluidized bed coating system. Solution was found to be suitable as a spraying solution for application of Itopride Hydrochloride. Specific issues affecting coating operation such as air flow, inlet temperature, bed temperature, distributor plate design, atomizing air pressure were optimized. Three trials were prepared (Table 1).

Evaluation parameters of pellets:
Evaluation parameter of drug loaded pellets are Appearance, Assay and Practical Yield

Step II: Polymer Coating
Preparation of Polymer Coating Solution/Suspension Steps:
Dissolve HPMC-15 cps in purified water (hot), Dissolve ethyl cellulose in Isopropyl Alcohol. Both the solution was mixed and stirred for 1-2 hours. Talc was added to the above solution. A white milky solution was obtained, which was then passed through using Nylon cloth of mesh No.200.

Polymer coating process:
Load the drug loaded microcrystalline cellulose (Celesphere CP 203) USP in the wurster product container. Set the coating machine as per the parameters mentioned above. Preheat the pellets until the product temperature reaches 35°C (Table 2). Once the preheating is over, start spraying of coating suspension continue the coating by monitoring operation critically to avoid clustering of Pellets and lump formation and ensure uniform fluidization of Pellets throughout the coating process. Promptly clear any blockage of nozzle, if any during spraying. The silicon tubes fitted in the spray pump should be monitored throughout the process for any breakage or rupture. After completion of spraying coating suspension, spray Purified water used to prepare the coating suspension. Dry the Polymer Coated Pellets in the product container for 30 minutes or until the product temperature reaches 45°C. Record the LOD using halogen moisture analyzer. It should be less than 2%. After complete drying, cool down to 30°C before unloading. Sift the Polymer Coated Pellets through # 40 S.S. sieves. Weigh the Polymer Coated drug Pellets and record the yield.

Evaluation parameters of pellets:
Following tests were performed to evaluate prepared pellets of Itopride Hydrochloride.

a) Flow properties:
The Carr Compressibility Index and Hausner ratio of the coated pellets were computed on the basis of bulk density and tapped density. 20 g of the pellets were poured gently through a glass funnel into a graduated cylinder exactly to 50 ml mark. Excess pellets were removed using a spatula and the weight of the cylinder with pellets was determined. Weight of the pellets required for filling the cylinder volume was calculated[6].

b) Size analysis:
The size analysis of the pellets (50gm) was performed with the help of sieve analysis. A sieve shaker was operated for 20 minutes to separate the pellets into various size fractions. The mass median diameter was employed to characterize the pellets size and size distribution[7].

c) Particle Morphology:
The shape and surface characteristic of the Itopride Hydrochloride containing pellets were evaluated by scanning electron microscopy using a stereo scan 360 microscope[8].

d) Aspect ratio:
Aspect ratio was done for the pellet's sphericity, for the flow property. Hot stage microscope was used for the measurement of the height and width of the pellets. Aspect ratio should be very near to 1 for the best spherical shape[9]. Aspect ratio was calculated from following formula[10]

$$\text{Aspect ratio} = \frac{\text{Length of pellets}}{\text{Width of pellets}}$$

e) Assay: % Assay of drug coated pellets was performed for checking the quantity of drug entrapped into selected quantity of pellets. % Assay was performed by UV method[11].

f) Practical Yield: Percent practical yield was calculated by the formula after completion of each layering process to see losses occurred during each step[12].

Compression of MUPS Tablets
The components of each formulation were weighed, mixed in double cone blender to ensure homogeneous mixing. The MUPS tablets were prepared on rotary table compression machine using 12 mm Standard biconvex. Eight trials were prepared (Table 4).

Evaluation of MUPS tablets:
Prepared MUPS S.R tablet was evaluated for post compression parameters like hardness, friability, weight variation, thickness, disintegration and content uniformity[13].

Dissolution Studies
The release rate of Itopride Hydrochloride from MUPS sustained release tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5 $^{\circ}$C and 75 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly for 24 h, and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution the amount of drug release was determined from the calibration curve [14].

RESULTS AND DISCUSSION

Drug loading:
Pellets containing Itopride Hydrochloride were prepared using the multifunction fluid bed coater, which is able to process pellets as well as micro granules. Spheres consisting Celesphere 203, with mean diameter of 250-300 µm having # 20/30 mesh fraction were chosen as inert seeds in order to obtain final pellets. The entire drug layering process was conducted as follows: Celesphere 203 spheres, used as inert seeds, were poured into coating vessel, and then intermittently treated with drug solution applied with spray guns.

Evaluation Parameter of Trials IT_1, IT_2, IT_3:
Appearance and Particle size distribution study:
Drug coating on the Celesphere 203 pellets with different proportion of binder concentration was evaluated. Three different concentration of binder was taken for drug coating. In IT_1, IT_2, IT_3 hypromellose concentration was used 3.5%, 4.5% and 6% respectively. But by appearance of all three batch pellets, IT_2 pellets were seen uniform in shape and size. And also the pellets of IT_2 had good flow than other batches. P.S.D. study of all three batches shown that drug coated pellets was retained highest on 40# sieve in IT_2 than other two batches. And also fines were very less observed in IT_2 than in IT_1 because in IT_1 less concentration of binder was used. Aggregation of pellets was also less in IT_2 than IT_3 because in IT_3 Binder concentration was higher than other batches. So, by appearance and Particle size it was concluded that IT_2 was used for next Sustained release coating on drug coated pellets (Table 5).

% Assay:
% Assay of drug coated pellets of three different batches was done by UV Visible spectroscopy analysis. Assay of drug coated pellets was done by taking 376, 382, 388 mg of pellets respectively from

three different batches such as IT_1, IT_2 and IT_3 and observed this qty of pellets for Itopride content. 150 mg of Itopride presence in three different batches. Means 100 % assay of pellets. Assay of three different batches was found distributed because of different proportion of binder concentration in different batches. In IT_1 assay was observed less but in IT_2 and IT_3 Assay was nearer to required assay. But IT_3 the pellets are sticking with each other and the appearance was not quite good. So, in IT_2, pellets were containing very nearer to required quantity of Itopride than other two batches. And the appearance also good. From the P.S.D data and % Assay data, it was concluded that IT_2 shows good drug entrapment and appearance of pellets with 4.5 % polymer used as a binder. So, for next polymer coating on drug coated pellets were done using IT_2 pellets (Table 6).

Evaluation Parameter of Polymer Coating on Drug Coated Pellets:

Flow property:

For excellent flow properties, Hausner's ratio and Carr Compressibility Index should be between 1.2 – 1.3 and 5 – 15, respectively (Table 7). It can be seen from results that prepared pellets having Hausner's ratio (1.07) and Carr Compressibility Index (7.16), which confirmed the free flowing nature of the coated pellets.

Appearance and particle size distribution study:

From the appearance and P.S.D. study of pellets, batch no. IT_2F2, IT_2F3, IT_2F7, IT_2F8 shown good pellets. In Batch IT_2F1& IT_2F5, IT_2F6 film coating on pellets was not completely done. In 5% ethyl cellulose and HPMC (75:25) and 3%, 5% ethyl cellulose and HPMC (85:15) concentration polymer film coating on pellets was observed not proper and also plasticity wasn't observed in pellets. Most of the film coated pellets have to retain on the 30 and 40# sieve with minimum fines. This criterion was only observed in B. No. IT_2F2, IT_2F3, IT_2F4, IT_2F7, IT_2F8. But in Batch IT_2F4 aggregation of pellets was observed in little amount and sticking of pellets occurred to the each other. So from appearance and P.S.D study, it was concluded that B. No. IT_2F2, IT_2F3, IT_2F7 and IT_2F8 show good pellets in comparisons with other batches (Table 8).

Shape analysis:

The shape analysis of the Celesphere, drug loaded pellets and polymer coated pellets obtained (Fig. 1). It was evident from SEM photo micrographs that Celesphere 203, drug loaded pellets and polymer coated pellets were discrete, spherical or oval with slightly rough surface. No significant change of shape was found in drug loaded pellets and polymer coated pellets as compare to Celesphere 203.

Aspect ratio:

Aspect ratio was done for the pellet's spherocity and it was found that the ratio of the pellets is 1.

% Assay, % yield and Content Uniformity:

% Assay and CU of all batches was acceptable and came in to the range, except batch IT_2F1. %assay & % CU results of all batches shown that all batch contain equivalent amount of Itopride Hydrochloride within range. But, Batch IT_2F4 shows the comparable and exact result of % assay & %CU. So, from the results it was concluded that Batch IT_2F4 and IT2F8 was good for sustained coating (Table 10).

CONCLUSION

In present investigation attempts were made to prepare 8 batches of multi unit particular tablets of Itopride Hydrochloride by using different polymers namely ethyl cellulose 50 cps and HPMC E-6 cps. The prepared tablets were evaluated for weight variation**,** thickness, %drug content, content uniformity, hardness disintegration time, *in* vitro drug release. The result of present study demonstrated that out 8 formulations, the formulation IT2F8 of Itopride Hydrochloride using HPMC and Ethyl cellulose in a ratio 85:15 in 9% was found to comply with marketed preparation (similarity Value is 92.73 and dissimilarity value is 1.44). The said formulation was found stable and dissolution profile of formulation under study was comparable with market tablets of Itopride Hydrochloride. In conclusion, the multi unit particular tablet of Itopride Hydrochloride (IT2F8) prepared using HPMC and Ethyl cellulose in a ratio 85:15 in 9% seems to be promising formulation and further in vivo study may be carried out.

Table 1: Trials for Drug Loading

Ingredients	Qty in Gram IT1	IT2	IT3
Base Pellet			
Celesphere 203 (20 – 25#)	175.5	175.5	175.5
Preparation of drug Coating Suspension			
Itopride Hydrochloride	150	150	150
Hypermellose 6 cps	8	10	13
Mag. Carbonate (light)	10	10	10
Pharma Grade Sugar	18	18	18
Maize Starch	11	11	11
Talc	4	7	10
Purified water	160	190	190
IPA	160	190	190
Expected Wt	376.5	381.5	387.5
Practical Wt	358.91	374.44	376.17
Practical Yield	95.32	98.14	97.06

Table 2: Process Parameter of FBP

Sr. No.	Parameters	Unit	Min.	Set.	Max.	Trip
		Preheating conditions.				
1	Temp. inlet air	°C	45	50	55	--
2	Temp. product	°C	25	--	35	45
3	Temp.exhaust	°C	25	--	35	45
		Wurster spraying condition				
4	Temp. inlet air	°C	37	45	50	--
5	Temp. product	°C	30		37	50
6	Press. atomization air	bar	1.8	2	2.2	--
		Drying conditions				
7	Temp. inlet air	°C	40	45	50	--

Table 3: Trials for Polymer Coating with Ethyl Cellulose and Hypermellose

Ingredients	E.C and HPMC (75:25)				E.C and HPMC (85:15)			
	IT2F1 (5%)	IT2F2 (8%)	IT2F3 (10%)	IT2F4 (12%)	IT2F5 (3%)	IT2F6 (5%)	IT2F7 (7%)	IT2F8 (9%)
DLP	381.5	381.5	381.5	381.5	381.5	381.5	381,5	381.5
HPMC15 cps	4.77	7.63	9.54	11.45	1.72	2.86	4.05	5.15
E.C 50 cps	14.3	22.89	28.61	34.34	9.73	16.22	22.7	29.18
Talc	5.34	5.34	5.34	5.34	5.34	5.34	5.34	5.34
Purified water	100	100	100	100	100	100	100	100
IPA	150	150	150	150	150	150	150	150
Expected Wt	405.91	417.36	425	432.63	398.29	405.92	413.59	421.17
Practical Wt	393.05	412.32	419.71	426.11	387.16	398.66	401.27	415.23
Practical Yield	96.83	98.79	98.75	98.49	97.2	98.21	97.02	98.58

DLP (Drug Loaded Pellets)

Table 4: Compression of MUPS Tablets

Ingredients	E.C and HPMC (75:25)				E.C and HPMC (85:15)			
	IT2F1 (5%)	IT2F2 (8%)	IT2F3 (10%)	IT2F4 (12%)	IT2F5 (3%)	IT2F6 (5%)	IT2F7 (7%)	IT2F8 (9%)
PCP	406	417	425	433	398	406	414	421
MCC101	173.38	167.88	163.88	159.88	177.38	173.38	169.38	165.88
DCL	173.36	167.86	163.86	159.86	177.36	173.36	169.36	165.87
Crospovidone	35	35	35	35	35	35	35	35
Talc	7	7	7	7	7	7	7	7
Aerosil	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
Total (mg)	800	800	800	800	800	800	800	800

PCP (Polymer coated pellet), DCL (Direct compressible lactose)

Table 5: Comparative P.S.D study of Drug loaded Pellet

Sieve no.	% wt retain of Pellets		
	IT1	**IT2**	**IT3**
20	0	0.7	0.81
30	0.4	2.1	7.99
40	49.7	77	73.9
60	26.3	17.1	13.2
80	14.4	1.3	2.3
100	3.5	0.7	0.6
Above 100 (Base)	5.7	1.1	1.2

Table 6: Evaluation of Batch IT_1, IT_2, IT_3

B. NO.	%Assay	% yield	Appearances
IT1	91.1	97.25	Good
IT2	98.6	98.23	Excellent
IT3	97.8	95.37	Sticking

Table7: Evaluation of Polymer Coated Pellets

Flow parameters	IT2F1	IT2F2	IT2F3	IT2F4	IT2F5	IT2F6	IT2F7	IT2F8
B.D (gm/ml)	0.713	0.714	0.693	0.718	0.699	0.784	0.793	0.779
T.D (gm/ml)	0.768	0.789	0.773	0.797	0.783	0.871	0.884	0.855
Carr's index (%)	7.16	9.5	10.34	9.91	10.72	9.98	10.29	8.88
Hausner's ratio	1.07	1.1	1.11	1.11	1.12	1.1	1.1	1.07

Table 8: Comparative P.S.D study of polymer coated Pellet

Sieve no.	% wt retain of Pellets							
	IT2F1 (5%)	**IT2F2 (8%)**	**IT2F3 (10%)**	**IT2F4 (12%)**	**IT2F5 (3%)**	**IT2F6 (5%)**	**IT2F7 (7%)**	**IT2F8 (9%)**
20	0.7	1.2	5.8	10.1	0.3	0.5	0.6	1.8
30	42.8	52.4	66.1	71.8	37.6	43	50.8	55.1
40	35.8	28.4	24.3	15.8	37.4	35.6	30.1	30.7
60	12.2	6.1	1.3	1.4	15.9	12.5	7.6	4.8
80	2.5	5.7	0.7	0.2	4.7	2.4	4.1	4.1
100	3.3	2.2	1.1	0	2.3	3.6	3.8	2.2
Base	2.7	4	0.7	0.6	1.8	2.4	3	1.3

Table 9: Aspect ratio of polymer coated Pellet

Bt. No.	Length (μm)	Width (μm)	Aspect ratio
IT2F1	1422	1369	1.038
IT2F2	1260.8	1212.3	1.04
IT2F3	1188	1103.2	1.076
IT2F4	1104.1	1077.8	1.024
IT2F5	1238.8	1169.5	1.059
IT2F6	1198.6	1145.6	1.0462
IT2F7	1345	1275.76	1.0542
IT2F8	1257.6	1211.3	1.0382

Table 10: % Assay, % yield and Content Uniformity of polymer coated Pellet

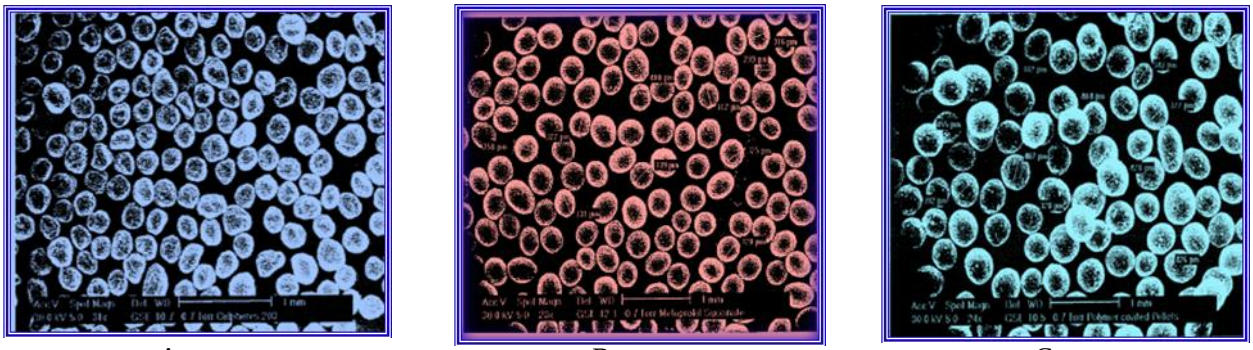
Bt. No.	Avg. % Assay	Avg. % CU	Avg. % Yield
IT2F1	93.1	95.8	97.96
IT2F2	103.3	104.3	98.75
IT2F3	101.8	102.8	98.43
IT2F4	99.8	100.2	98.13
IT2F5	98	98.4	98.48
IT2F6	99.1	99.4	98.54
IT2F7	101.3	100.3	98.29
IT2F8	98.7	98.2	98.5

Table 11: Post compression parameter of MUPS Tablet

Code	Wt. Variation (mm±SD) N=20	Thickness* (mm±SD) N=10	Hardness* (Kg/cm^2) N=10	DT (minutes) N=6	Friability (%)
IT2F1	800±0.86	6.5±0.85	7.1±0.84	6.43±0.19	0.29
IT2F2	803±0.69	6.4±0.12	7.8±0.36	6.41±0.17	0.47
IT2F3	804±0.97	6.5±0.39	6.9±0.68	6.5±0.41	0.49
IT2F4	801±1.04	6.4±0.86	6.9±0.34	6.5±0.41	0.62
IT2F5	801±0.66	6.4±0.42	7±0.71	6.49±0.39	0.39
IT2F6	802±0.34	6.5±0.39	6.7±0.89	6.5±0.39	0.61
IT2F7	803±0.57	6.5±0.71	7.1±0.13	6.8±0.26	0.41
IT2F8	801±0.69	6.4±0.82	7.2±0.71	6.13±0.44	0.38

Table 12: In–Vitro Release study of Innovator and Prototype Formulation

Time Hrs	IRP	E.C and HPMC (75:25)				E.C and HPMC (85:15)			
		IT2F1 (5%)	IT2F2 (8%)	IT2F3 (10%)	IT2F4 (12%)	IT2F5 (3%)	IT2F6 (5%)	IT2F7 (7%)	IT2F8 (9%)
1	21.33	41.6	36.6	27.6	16.4	39.6	32.5	26.5	21.5
2	37.74	68.8	62.8	56.1	31.5	57.8	54.1	43.5	39.5
6	58.41	90.8	81.8	72.2	52.5	72.4	70.1	64.2	59.1
12	76.92	98.5	94.5	89.1	71.6	81.9	80.5	78.9	76.8
18	89.08	100.3	98.3	99.2	81.5	99.4	97.5	94.6	87.7
24	99.29	1.2	101.4	100	95.3	100.7	100.2	99.3	97.9



A B C

Figure 1: Scanning electron microscope of (A) Celesphere 203 (B) drug loaded pellets and (C) polymer coated pellets

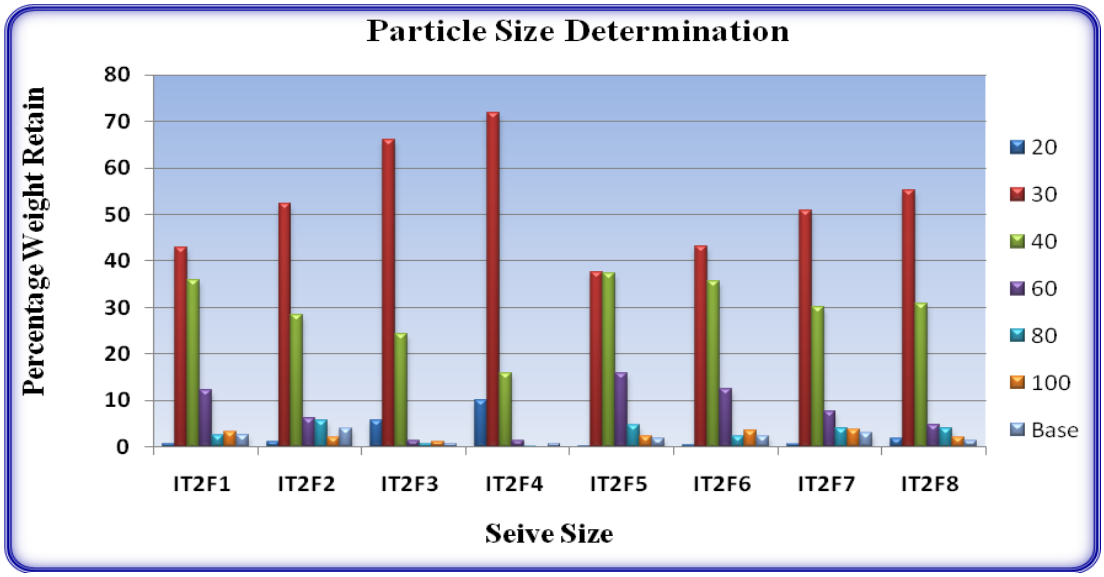
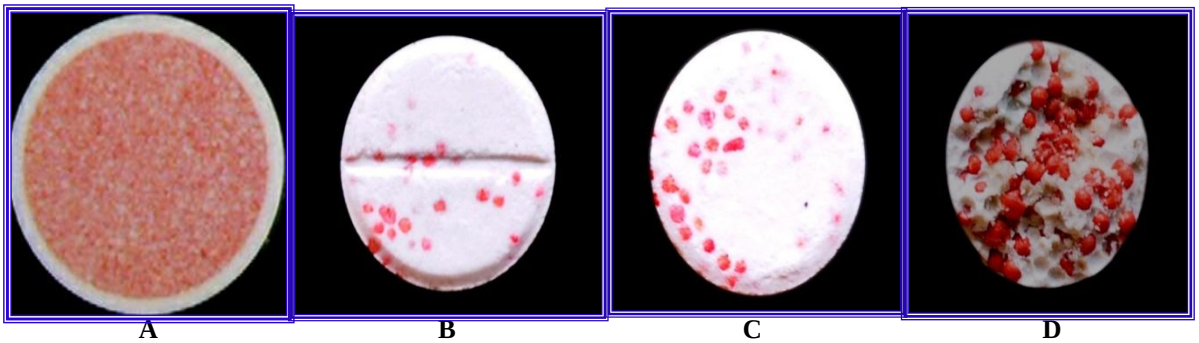


Figure 2: P.S.D. Study of IT_2F1- IT_2F8



A B C D

Figure 3: Photograph (A) indicate coated pellets, Photograph (B) indicates the upper surface of tablet, Photograph (C) indicate the lower surface of tablet, Photograph (D) indicate the middle part of tablet, in which the pellets are uniformly distributed, After compression of tablet the pellets still retain its original shape and size.

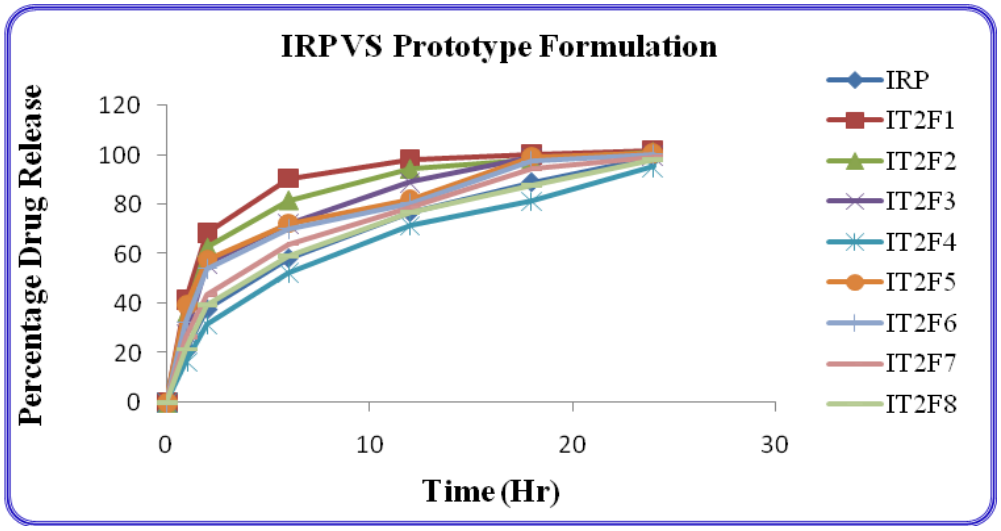


Figure 4: Comparatative drug release profile of Innovator Vs MUPS Formulations

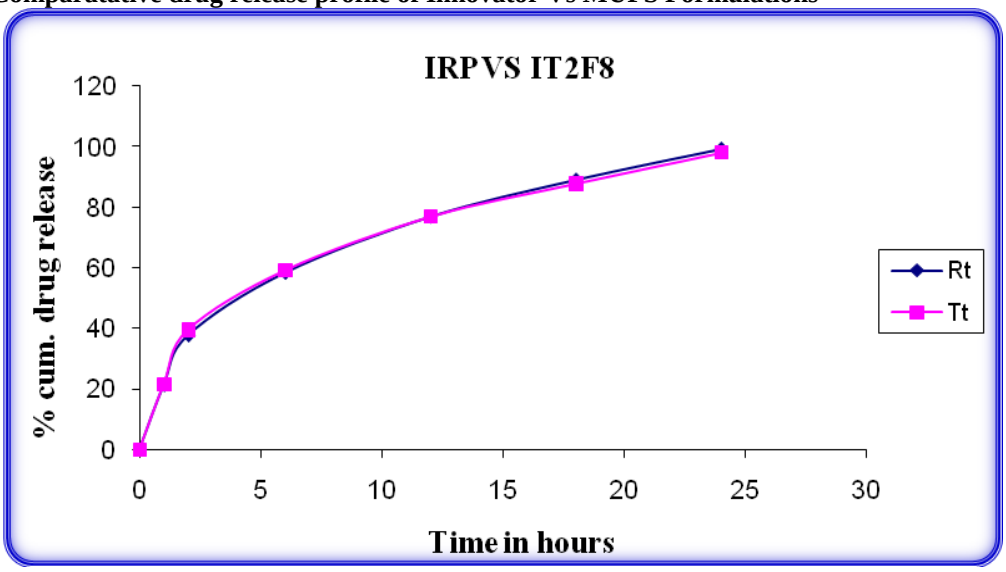


Figure 5: Comparatative drug release profile of Innovator (Rt) Vs IT2F8 (Tt)

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