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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF IRBESARTAN AND ATORVASTATIN CALCIUM.

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ABSTRACT

Fast Dissolving Tablets (FDT)) are most accepted and exploited drug delivery for the patients who are having difficulty with swallowing i.e., mainly and Geriatric's. Irbesartan (IRB) is an anti-hypertensive and it is also used in many Coronary artery diseases, Where As Atorvastatin Calcium (ASC) is an anti-hyperlipidemic that prevents of Atheroma. The aim of the paper was to formulate a combined oral dosage form of Irbesartan and Atorvastatin calcium into fast dissolving tablet using three super disintegrants such as Croscarmellose Sodium (CCS), Crosspovidone (CP), Sodium Starch Glycolate (SSG) at various concentrations to enhance the disintegration and dissolution of IRB and ASC to improve bioavailability of the drugs. The tablets were prepared by using direct compression method and evaluated for weight variations, Hardness, Friability, Wetting time, Disintegration time and Dissolution study. Prepared tablets are subject to FT-IR Study for Characterization and compatibility study. No Chemical interaction between drug and excipients were indicated in the FT-IR. Disintegration and dissolution profiles decreases with addition of super disintegrating agents like Croscarmellose Sodium (CCS), Cross povidone (CP), Sodium Starch Glycolate (SSG). Among all the formulation F6 with CP in 5% Concentration found to be best in drug release profile. The results showed that superdisintegrants used in single shows better disintegrating property. Among all formulations, promising formulation F6 showed good wetting time (40 sec), fastest disintegration time (52 sec) and maximum drug release of 95.66%(ASC) and 89.24%(IRB) within 45 minutes.

KEYWORDS: Irbesartan, Atorvastatin, Antihypertensive, Antihyperlipidemic, Wetting time.

INTRODUCTION

In recently, two major problems are being observed in among people like hypertension and hyperlipidemia. So, Irbesartan is used in combination with Atorvastatin Calcium to treat hypertension and hyperlipidemia, respecitvely, in cardiovascular patients. Fast dissolving tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that dysphagia (difficulty in swallowing) is common among all age groups and more specific with geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. FDTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Many hypertensive symptoms of hyperlipidemia patients may be reduced using the combination formulation of antihyperlipidemic and antihypertensive agents. Combined dosage form of two or more drugs has been proven useful in multiple therapies as they offer better patient compliance than a single drug. There are various methods to prepare FDT which are conventional methods like wet granulation technique,moulding technique, direct compression method etc., in which direct compression is used in the present study. These tablets were prepared with very low compression force. As there is increase in compression they may affect the hardness of the tablets, which in turn may show its effect on disintegration. These Fast dissolving tablets doesn't need water because they could able to dissolve rapidly in the saliva of the mouth. When we kept on the tongue they could easily disintegrate and release the drugs. Some drugs are usually absorbed from the pharynx. While the saliva passes into the stomach.[1-3]

The drugs which were used in the present study are comes under anti-hypertensive and anti-hyperlipidaemia category and water insoluble drugs. In order to improve the solubility and fast reliving, by using this fast dissolving tablets the bioavailability and immediate release would be produced. In the present study Irbesartan and Atorvastatin calcium are having low solubility in water. There solubility and their disintegration, Dissolution rate is increased by incorporating super disintegrating agent like Croscarmellose Sodium, Crosspovidone, Sodium Starch Glycolate increasing concentration.[4-6]

MATERIALS AND METHODS

Irbesartan and Atorvastatin Calcium were received as gift samples From Aurobindo Pvt.Ltd. and Wockhardt Lvt. Aurangabad respectively. Microcrystalline cellulose, Crosspovidone and Sodium Starch glycolate, Croscarmellose sodium, Magnesium Stearate, Sodium Carbonate, Talc, Mannitol, Vannila are obtained from commercial sources and all the reagents used are of analytical grade.

Methodology

Fast dissolving tablets of Irbesartan and Atorvastatin Calcium is prepared by geometric mixing. All the ingredients were weighed according to the formula in Table No. 1. Nine formulations containing Crosspovidone, croscaramellose sodium and Sodium Starch Glycolate alone, in combination and in different concentrations were prepared by direct compression method in a single stage tablet punching machine.[7-9]

A batch of 50 tablets was prepared in each batch for further characterization. Standard deviation (SD), averages.

Table 1: Formulation of Fast Dissolving tablets of Irbesartan and Atorvastatin calcium using direct compression technique.

Sr. No.	Ingredients	Quantities in mg per tablet								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Irbesartan	75	75	75	75	75	75	75	75	75
2.	Atorvastatin Calcium	10	10	10	10	10	10	10	10	10
3.	Croscarmellose Sodium	10	10	20	-	-	-	-	10	-
4.	Crosspovidone	-	10	-	10	10	20	-	-	-
5.	Sodium Starch Glycolate	-	-	-	-	10	-	10	10	20
6.	Microcrystalline Cellulose	261	251	251	261	251	251	261	251	251
7.	Sodium Carbonate	32	32	32	32	32	32	32	32	32
8.	Talc	4	4	4	4	4	4	4	4	4
9.	Magnesium Stearate	4	4	4	4	4	4	4	4	4
10	Mannitol	2	2	2	2	2	2	2	2	2
11	Vanilla	2	2	2	2	2	2	2	2	2
12	Total weight of tab	400	400	400	400	400	400	400	400	400

A. Evaluation of Fast Dissolving Tablets of Irbesartan and Atorvastatin calcium.

Pre- Compression Parameters

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$\text{Tan}\theta = h / r$

$\theta = \text{Tan} -1\ h / r$

Where, θ = angle of repose, h = height, r = radius.

Bulk Density

The ratio of mass (weight) to volume is known as the bulk density of material.

The equation for determining the bulk density is,

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of sample in mg}}{\text{Volume Occupied by sample in ml}}$$

Tapped Density

Using the weight of drug in cylinder and tapped volume, the tapped density is determined.

$$\text{Tapped density (g/ml)} = \frac{\text{Weight of sample in gm}}{\text{Tapped Volume occupied by sample in ml}}$$

Compressibility Index (Carr's index)

The Carr's index is determined from the tapped density and poured density (bulk density) as per the formula:

$$\text{Carr's index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}$$

Hausner's Ratio

Hausner's ratio is determined from the ratio of tapped density to bulk density using formula given below.

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Fourier Transform Infrared Spectroscopy

To check the compatibility of drugs with each other and with superdisintegrants, Fourier transform infrared spectroscopy was conducted. Sample preparation was done in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400–4000 cm-1 and the resolution was 2 cm-1.The hydraulic pressure was kept 150kg/cm.[2]

B. Post Compression Parameters

Quality control tests for FDTs of all formulations were performed, and the average values were calculated. All the tablets were evaluated for different parameters as weight variation, hardness, friability, drug content, wetting time, water absorption ratio, disintegration time and in vitro dissolution study.

Weight Variation: In a weight variation test twenty tablets were selected at random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight.

Tablet Hardness: For Tablet hardness testing. It is done by using Pfizer hardness tester. Selected tablet was placed in between the plungers and the handle was pressed, the force of fracture was recorded. The friability of the tablets was determined using Lab India friabilator.

Disintegration Time: The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications.

Wetting Time: In wetting time a piece of tissue paper folded twice was placed in small petri dish (i.d=6.5cm) containing 6mL of water, a tablet was placed on the paper, and the time for complete wetting was measured.

Three trails for each batch were performed and standard deviation was also determined.

Water absorption ratio

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water
absorption ratio, R was determined according to the following equation.

$R = 100 (Wa – Wb) / Wb$

Where, Wb and Wa are the weight before and after water absorption, respectively.

***In vitro* dissolution testing**

Dissolution study was conducted for all the formulation using USP type-II apparatus. The dissolution test was performed using 900 ml of 0.1 N HCL was taken as the dissolution medium at 50 rpm and 37ºC±0.50C.. The samples were analyzed spectrophotometrically at 242&249 nm.

Stability Studies

Stability studies were carried out for the optimized formulation according to ICH guidelines. An optimize formulation were sealed in aluminium packaging coated inside with polyethylene, and samples were kept in humidity chamber (Remi, India) at 40°C and 75% RH for three month. At the end of the three month, samples were analyzed for drug physical changes, properties, drug content and in vitro release studies.

RESULTS AND DISCUSSION

Fast Dissolving tablets of Irbesartan and Atorvastatin Calcium of Strength 75 &10 mg respectively were prepared by using direct compression method with three superdisintegrant such as Croscarmellose Sodium (CCS), Cross Povidone (CP) and Sodium Starch Glycolate (SSG).

Nine formulations containing Crosspovidone, crosscaramellose sodium and Sodium Starch Glycolate alone, in combination and in different concentrations 2.5%, 5% used to study the effect of concentration on formulation Dissolution profile.

Before compressing, powder blend was first assessed for rheological properties. The results had shown that all the parameters were present within the specified limits. It indicates that powder has good flow properties. This powder blend was used to make Fast dissolving tablets.

The weight of tablets was present between 395.5 to 400.15 mg. This indicates that tablets have no weight variation. Friability of all 9 formulations was less than 1% which indicates that tablets had good mechanical strength to bear any sort of stress during transport and storage.

Disintegration time (55 to 180 sec), wetting time (40 to 82 sec) and dispersion time (52 to 82 sec) were calculated for each formulation. Tablets should disintegrate completely in oral cavity in less than 3 minutes. The fast disintegration may be due to the rapid uptake of water from the medium which results in swelling and bursting effect is produced. Disintegration time, wetting time and dispersion time all were less for F6 formulation containing Crosspovidone. Water Absorption ratio was used to determine that how much water is absorbed by the tablets. As value of water absorption ratio increases it indicates that rapid breaking of tablets and there fore faster disintegration as table 4. This disintegration ultimately affect dissolution rate of tablets. It was more for the formulations containing crosscaramellose sodium than crosspovidone. The drug release studies were performed up to 45 minutes at 242and 249nm for Irbesartan and Atorvastatin respectively using UV- visible spectrophotometer after appropriate dilution and filtration. Drug release was rapid for F6 formulation that was 95.66% for atorvastatin and 89.24% for Irbesartan within 45 min. Three best formulations were chosen for stability studies. No significant changes were occurred in various parameters at the end of three months when stability studies were performed under zone 4 according to ICH (International Conference on Harmonization) guidelines.

Table 2: Pre-compression studies parameters of Fast Dissolving Tablet of Irbesartan and Atorvastatin calcium.

Batch	Angle of repose(θ)	Bulk Density(gm/cm^2)	Tapped Density(gm/cm^2)	Carr's Index
F1	26.06±0.04	0.8221±0.03	0.9247±0.02	12.48
F2	24.67±0.01	0.864±0.02	0.9234±0.04	11.73
F3	28.08±0.02	0.845±0.02	0.9916±0.01	9.67
F4	27.08±0.01	0.8321±0.02	0.9221±0.02	10.81
F5	23.67±0.02	0.8284±0.03	0.9286±0.04	11.96
F6	25.55±0.0227	0.837±0.02	0.9335±0.02	10.33
F7	28.08±0.01	0.8439±0.04	0.9321±0.02	9.49
F8	26.06±0.04	0.8294±0.02	0.9296±0.03	12.08
F9	24.85±0.01	0.8221±0.03	0.9247±0.02	12.48

Table 3: Post-compression studies of Fast Dissolving Tablet of Irbesartan and Atorvastatin calcium.

Batch	Weight Variation(%) ±SD,n=20	Friability (%) ±SD,n=20	Hardness (Kg/cm^2) n=3	Thickness (mm) n=3	Drug Content (%)
F1	400.05	0.88±0.03	6.5	4.3	90.11(ASC)
					84.25(IRB)
F2	395.50	0.66±0.03	6.5	4.3	90.58(ASC)
					86.05(IRB)
F3	399.45	0.48±0.03	6.0	4.4	87.44(ASC)
					84.30(IRB)
F4	400.10	0.41±0.01	6.5	4.2	81.42(ASC)
					76.71(IRB)
F5	397.25	0.54±0.01	6.5	4.4	84.57(ASC)
					78.21(IRB)
F6	400.07	0.66±0.03	6.0	4.3	95.33(ASC)
					89.04(IRB)
F7	395.88	0.8±0.04	6.5	4.3	72.65(ASC)
					68.26(IRB)
F8	398.49	0.60±0.02	6	4.4	83.79(ASC)
					81.37(IRB)
F9	400.15	0.54±0.01	6	4.2	89.55(ASC)
					83.87(IRB)

Table 4: Post-compression studies of Fast Dissolving Tablet of Irbesartan and Atorvastatin calcium.

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dispersion time(Sec)	80	65	82	60	55	52	65	55	55
Wetting time(Sec)	82	80	52	42	42	40	55	52	50

Table 5: Dissolution profile and percentage of drug release of Fast Dissolving Tablet of Irbesartan and Atorvastatin calcium.

Formulation		5min	10min	15min	25min	35min	45min
F1	ASC	28.52	59.82	74.70	78.88	85.16	90.90
	IRB	27.87	56.65	67.09	74.55	77.78	85.44
F2	ASC	30.07	61.38	73.52	77.77	84.07	91.19
	IRB	29.17	58.46	68.33	74.24	79.19	86.47
F3	ASC	40.36	68.25	74.20	81.48	84.34	88.22
	IRB	38.83	64.38	69.80	75.46	81.49	84.65
F4	ASC	14.48	49.48	71.05	76.02	79.43	81.67
	IRB	15.77	47.68	67.44	72.02	75.10	77.17
F5	ASC	32.68	61.29	74.63	77.60	80.66	84.22
	IRB	32.08	58.34	70.65	73.29	76.01	79.25
F6	ASC	30.55	62.41	82.10	87.71	92.85	95.66

	IRB	30.01	56.05	76.94	81.68	86.94	89.24
F7	ASC	11.45	13.23	29.36	55.84	66.82	72.00
	IRB	13.32	14.79	29.55	53.68	56.65	68.43
F8	ASC	19.51	27.63	51.21	64.17	80.55	84.68
	IRB	19.76	27.35	49.83	61.55	75.62	81.45
F9	ASC	19.83	38.42	51.81	67.89	78.64	89.64
	IRB	20.30	36.04	52.47	67.60	76.39	83.89

Table 6: Stability study (40 °C/75%RH) of Optimized Formulation (F6) of Fast Dissolving Tablet of Irbesartan and Atorvastatin calcium.

Parameters	Before Stability study	After Stability study
Weight variation(mg)	400.08	400
Hardness (kg/cm2)	6.5	6.3
Friability(% w/w)	0.66	0.70
In vitro disintegrating time(sec)	60	54
Wetting time(sec)	40	38
Drug content (%)	95.33	95.15
In vitro release (%) at 45 min	95.66	95.32

CONCLUSION

Fast Dissolving tablets of Irbesartan and Atorvastatin calcium were prepared by direct compression method using crosspovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) in individual and combined form as CP and CCS in combination of 10:10 and ratios, CP and SSG in combination of 10:10 ratios and CCS and SSG in combination of 10:10 ratios respectively.

F6 prepared with Crosprovidone(20mg) as superdisintegrant released showed 95.66% for Atorvastatin calcium and 89.24% Irbesartan drug release respectively within 45 min and disintegrate within 52 Sec and also superior in all respect such as physico-chemical parameter, stability & drug released. Thus, F6 was considered as the best among the other formulations.

Other permutation combination selected for a various trials are compared with formulation F6, which has shown better characteristic than all remaining formulation from F1 toF9.

There for we can conclude that Crosspovidone 20mg with drug Atorvastatin calcium & Irbesartan is the best combination for Formulation & development of Fast dissolving tablet.

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