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Comparitive Evaluation of Fast Dissolving Tablets of Irbesartan Prepared By Wet Granulation and Sublimation Method.

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ABSTRACT

In the present study, an attempt has been made to find the best formulation by comparative evaluation of fast dissolving tablets of Irbesartan prepared by two different methods namely wet granulation and sublimation technique. Fast dissolving tablets of Irbesartan are prepared with a simple idea of improving the patient compliance. In the wet granulation method, tablets were prepared using superdisintegrants namely sodium starch glycollate (1,2,3,4%w/w) and Crosscarmellose (3,4%w/w) in different concentrations. In sublimation method, camphor was used as subliming agent along with different concentrations of crospovidone (2,4,6,8% w/w). The tablets thus prepared were evaluated for weight variation, hardness, friability, drug content uniformity, wetting time, water absorption ratio, in vitro dispersion time and in vitro dissolution studies. Short-term stability studies (40±2º/75±5% RH for 3 months) and drug-excipient interaction studies were performed for best formulation (invitro dispersion time less than 15secs for WG_3 and SB_3). In vitro dissolution study results showed that tablets prepared by sublimation technique showed faster drug release when compared to tablets prepared by wet granulation method (% drug release in 5mins 78.6 and 76.9 respectively). IR spectroscopic study results showed that there is no drug excipient interaction. Short-term stability studies on the best formulations showed that there are no significant changes in drug content and in vitro dispersion time ($p<0.05$).

Keywords: Irbesartan, fast dissolving tablets, wet granulation method, sublimation method, superdisintegrants.

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INTRODUCTION

Oral drug delivery is the most common and preferred route of administration because of its wide acceptance. As there is an enhanced demand for more patient compliance dosage forms, the demand for new technologies has been increased three-fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are now focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects[1].Category of patients who experience problems in using conventional oral dosage forms include the mentally ill, uncooperative[2] and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing and choking[3]. Sometimes it may be difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called mouth dissolving tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water. Superdisintegrants added in the formulation increase the drug release, thus increasing the bioavailability of drug [4]. Techniques that are frequently employed in the preparation of mouth dissolving tablets include, freeze drying, sublimation, spray drying, moulding, mass extrusion and direct compression [5].

In the present study, fast dissolving tablets of Irbesartan (IB) which is used in the management of hypertension including the treatment of renal disease in hypertensive diabetic patients and prescribed for elderly patients in hypertension i.e., a lower initial dose of 75mg once dialy, for patients over 75yrs with intravascular volume depletion and for those receiving haemodialysis [6] were prepared by two different methods namely wet granulation and sublimation and are evaluated by various parameters and the results are compared.

MATERIALS AND METHODS

Materials

Irbesartan was received as a gift sample along with Crosspovidone, Crosscarmellose Sodium, Sodium starch glycollate and strawberry flavor from a MNC in Hyderabad. Mannitol, Camphor, Magnesium stearate and Methanol were procured from S.d fine chem.Ltd. Mumbai. Aerosil Procured from Himedia laboratories Ltd., Mumbai, PVP from Loba chemie Pvt Ltd., Mumbai, Aspartame from CDH Lab. Reagent. New Delhi.

Preparation of Orodispersible Tablets

By Wet Granulation Method

Irbesartan fast dissolving tablets were prepared by wet granulation method according to the formulae given in Table 1. Active Pharmaceutical Ingredient is mixed with intragranular disintegrant and diluents along with Aspartame. Allow it to pass through 40 mesh. To this mixture, add PVP solution (using IPA). Pass through 30 mesh, dry it. Again pass through 30 mesh. Calculate % yield, accordingly adjust extragranular excipients (disintegrant and diluent) and add to above granules, which is previously sifted through 30mesh. Blend

this mixture at 24rpm for 10 min. Then add aerosil, magnesium stearate, flavor(strawberry), which is previously sifted through 60 mesh screen to the above mixture and blend at 24 rpm for 5 min. Individually weigh for each tablet and compress using 7mm flat round punch tablet punching machine.

S.No	INGREDIENTS (mg)	FORMULATION CODE				
		WG_0	**WG_1**	**WG_2**	**WG_3**	**WG_4**
1	Irbesartan	75.0	75.0	75.0	75.0	75.0
2	Pearlitol SD 200 (Mannitol)	159	149	146.5	141.5	139
	Intragranular	63.6	59.6	58.6	56.6	55.6
	Extragranular	95.4	89.4	87.9	84.9	83.4
3	Aspartame	5.0	5.0	5.0	5.0	5.0
4	PVP k-30	5.0	5.0	5.0	5.0	5.0
5	Aerosil	0.5	0.5	0.5	0.5	0.5
6	Magnesium stearate	2.5	2.5	2.5	2.5	2.5
7	Cross carmellose sodium	0	7.5	7.5	10	10
	Intragranular	0	3.0	3.0	4.0	4.0
	Extragranular	0	4.5	4.5	6.0	6.0
8	Sodium starch glycollate	0	2.5	5.0	7.5	10
	Intragranular	0	1.0	2.0	3.0	4.0
	Extragranular	0	1.5	3.0	4.5	6.0
9	Flavour (strawberry)	3.0	3.0	3.0	3.0	3.0
TOTAL WEIGHT		250	250	250	250	250

Table 1: Composition of different batches of fast dissolving tablets of Irbesartan prepared by wet granulation method

By Sublimation Method

S.No	INGREDIENTS (mg)	FORMULATION CODE				
		SB_0	**SB_1**	**SB_2**	**SB_3**	**SB_4**
1	Irbesartan	75.0	75.0	75.0	75.0	75.0
2	Pearlitol SD 200 (Mannitol)	119	114	109	104	99.0
	Intragranular	47.6	45.6	43.6	41.6	39.6
	Extragranular	71.4	68.4	65.4	62.4	59.4
3	Aspartame	5.0	5.0	5.0	5.0	5.0
4	PVP k-30	5.0	5.0	5.0	5.0	5.0
5	Aerosil	0.5	0.5	0.5	0.5	0.5
6	Magnesium stearate	2.5	2.5	2.5	2.5	2.5
7	Cross povidone	0	5.0	10	15	20
	Intragranular	0	1.5	3.0	4.5	6.0
	Extragranular	0	3.5	7.0	10.5	14.0
8	Camphor	40	40	40	40	40
9	Flavour (strawberry)	3.0	3.0	3.0	3.0	3.0
TOTAL WEIGHT		250	250	250	250	250

Table 2: Composition of different batches of fast dissolving tablets of Irbesartan prepared by sublimation method.

Irbesartan fast dissolving tablets were prepared by sublimation method according to

the formulae given in Table 2. Active Pharmaceutical Ingredient is mixed with intragranular disintegrant and diluents along with Aspartame and camphor. Allow it to pass through 40 mesh. To this mixture, add PVP solution (using IPA). Pass through 30 mesh, dry it. Again pass through 30 mesh. Calculate % yield, accordingly adjust extragranular excipients (disintegrant and diluent) and add to above granules, which is previously sifted through 30mesh. Blend this mixture at 24rpm for 10 min. Then add aerosil, magnesium stearate, flavor (strawberry), which is previously sifted through 60 mesh screen to the above mixture and blend at 24 rpm for 5 min. Individually weigh for each tablet and compress using 7mm flat round punch tablet punching machine. The compressed tablets were then subjected to sublimation at 60^0C for 6 hours using hot air oven. Tablets were weighed at an interval of 1hr to check for weight difference which is because of evaporation of subliming agent[7].

Fig. 1: Formulation SB_3 (a) before sublimation and (b) after sublimation, Magnification (1X 6)

Evaluation of Mouth Dissolving Tablets

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation[8]. Hardness and friability of the tablets were determined by using Monsanto Hardness Tester and Roche friabilator respectively. Preweighed sample of ten tablets was placed in the friabilator, which was then operated for 4 min at 25 rpm. Tablets were dusted and reweighed. % loss in the weight of the tablets was calculated[8].

Ten tablets were weighed and powdered. The powder equivalent to 75 mg of IB was extracted into methanol and liquid was filtered. The IB content was determined by measuring the absorbance at 244 nm after appropriate dilution with methanol. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations[9].

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter of 5 cm) containing 6 ml of water. A tablet was put-on the paper and the wetted tablet was then weighed. Water absorption ratio 'R' was determined using following equation:

$$R = 100 \times \left(\frac{Wb - Wa}{Wa} \right)$$

Where Wa is weight of tablet, before water absorption and Wb is weight of tablet after water absorption [10].

One tablet was placed in a beaker containing 10 ml of phosphate buffer pH 6.8 at 37±0.5ºC and the time required for complete dispersion was measured[11]. The results are shown in Table 4**.**

In vitro dissolution of Irbesartan fast dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Cintex, Model-VFT-2D) employing a paddle stirrer at 50 rpm using 1000 ml of 0.1N HCl at 37±0.5^{0}C as dissolution medium[12]. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 244 nm. The volume withdrawn at each time interval was immediately replaced with fresh quantity of dissolution medium. Cumulative percent of IB released was calculated and plotted against time. The results are given in Table 5 and fig.2. IR spectra of IB and its formulations were obtained by KBr pellet method using Perkin Elmer FTIR series model-1615 spectrophotometer in order to rule out drug-carrier interaction.

Short-term stability studies on the promising formulations (WG_3 and SB_3) were carried out by storing 10 tablets in amber colored rubber stopper vials at 40±2º/75±5% RH over a period of 3months. At intervals of one month, the tablets were examined for any physical changes, changes in drug content and In vitro dispersion time.

RESULTS AND DISCUSSION

Comparative evaluation of Fast dissolving tablets of IB prepared by wet granulation and sublimation techniques was performed. IR spectroscopic studies indicated that there is no drug-excipient interaction. The pure drug IB has displayed characteristic peaks at 1620.56 cm–1 and 1064.92 cm–1 due to carbonyl and sulphoxide functional groups respectively. The IR spectrum of the overall promising formulation (SB_3) has shown all the characteristic peaks of irbesartan pure drug and thus confirming the undisturbed structure of the drug in the formulation.

Four different batches of formulations were designed in each method along with a control formulation which is devoid of the super-disintegrants. The mixture of drug and excipients in both the cases, was found to be free flowing and the results are given in Table 3.

S.No	Formulation Code	Angle of repose (^{0})	Carr's index(%)	Hausner's ratio	Rate of flow(g/sec)
1	**WG_0**	25	0.76	0.80	1.31
2	**WG_1**	20	0.79	0.80	1.31
3	**WG_2**	18.75	0.60	0.84	1.80
4	**WG_3**	18.75	0.60	0.84	1.50
5	**WG_4**	18.75	0.60	0.84	1.89
6	**SB_0**	19	0.80	0.69	2.00
7	**SB_1**	18	0.72	0.71	0.94
8	**SB_2**	10	0.66	0.90	0.95
9	**SB_3**	25	0.60	0.75	1.26
10	**SB_4**	18	0.54	0.80	1.28

Table 3 Pre-compression parameters for various formulations.

All the batches of tablets complied with the specifications for uniformity of weight. Drug content of the formulation was found to be in the range of 97.2 to 100.1 percent of the expected IB content, which was within the acceptable limits. The hardness of the tablets prepared by sublimation method (2.5 to 2.9 kg/cm^2) was less than those prepared by wet granulation method (2.9 to 3.2 kg/cm^2) because of their porous structure which are generated due to evaporation of camphor (Fig.1) Friability value below 1% was an indication of good mechanical resistance of the tablets against abrasion and mechanical shock during transport. Water absorption ratio, which helps in understanding the capacity of disintegrants to absorb water and swell in presence of it, was found to be in the range of 80 to 86.9%. Formulations WG_3 and SB_3 were found to be promising and displayed an in vitro dispersion time of 15 sec, which facilitates their faster dispersion in the oral cavity. Among the tablets prepared by wet granulation method, formulation WG_3 containing 3% w/w and 4% w/w concentration each of sodium starch glycollate and croscarmellose sodium, was found to be promising with an in vitro dispersion time of 15 sec against 300sec for control formulation (WG_0), which does not contain superdisintegrant (Table 4). Among the various tablet formulations prepared by sublimation method, formulation SB_3 containing 6% w/w crospovidone was found to be promising and showed in vitro dispersion time of 15 sec and water absorption ratio of 86.9% compared to the control formulation (SB_0), which showed 270 sec, and 80% values respectively for the same parameters (Table 4).

Formulation Code	Weight variation (%)	Hardness (kg/cm^2)*	Friability (%)	Wetting time(sec)*	Invitro dispersion time(sec)*	Water absorption ratio*	Uniformity of drug content(mg)*
WG_0	1.0	2.9±0.21	0.9	180±0.42	300±0.87	80.0±0.49	75.1±0.56
WG_1	1.1	3.2±0.10	0.8	34±0.35	21±0.39	83.3±0.55	72.0±0.79
WG_2	1.4	2.5±0.14	0.4	43±0.87	65±0.22	80.9±0.87	73.9±0.43
WG_3	1.2	2.6±0.37	0.0	9±0.40	15±0.91	86.0±0.56	74.8±0.73
WG_4	1.9	2.8±0.29	0.4	11±0.13	30±0.12	80.2±0.29	74.6±0.29
SB_0	1.0	2.9±0.70	0	190±0.29	250±0.74	81.2±0.97	74.2±0.17
SB_1	1.1	2.5±0.44	0	15±0.54	26±0.65	82.4±0.53	73.8±0.50
SB_2	1.4	2.5±0.54	0	10±0.77	23±0.48	82.9±0.42	72.9±0.26
SB_3	1.2	2.6±0.28	0	6±0.63	15±0.51	86.9±0.69	73.5±0.18
SB_4	1.9	2.7±0.20	0	8±0.31	28±0.89	84.0±0.35	73.7±0.39

*Average of three determinations; SD- Standard deviation

Table No. 4 Post-compression parameters for various Irbesartan tablet formulations

In vitro dissolution studies on the formulations, control along with pure drug (IB) were carried out in 0.1N HCl and the various dissolution parameter values, viz., percent drug dissolved in 10 min (D10%), time required for 50% and 70% drug release (t50% and t70%) are shown in table 5 and the dissolution profiles depicted in fig 2. From the data it is revealed that the formulation prepared by sublimation method (SB_3) displayed the best results (in vitro dispersion time 15 sec and %drug released in 5min is 78.6), over formulation prepared by Wet granulation method (WG_3) (in vitro dispersion time 15 sec and %drug released in 5min is 76.9). Short-term stability study results of the promising formulation indicated that there were no significant changes in drug content and in vitro dispersion time at the end of 3 months period ($p<0.05$).

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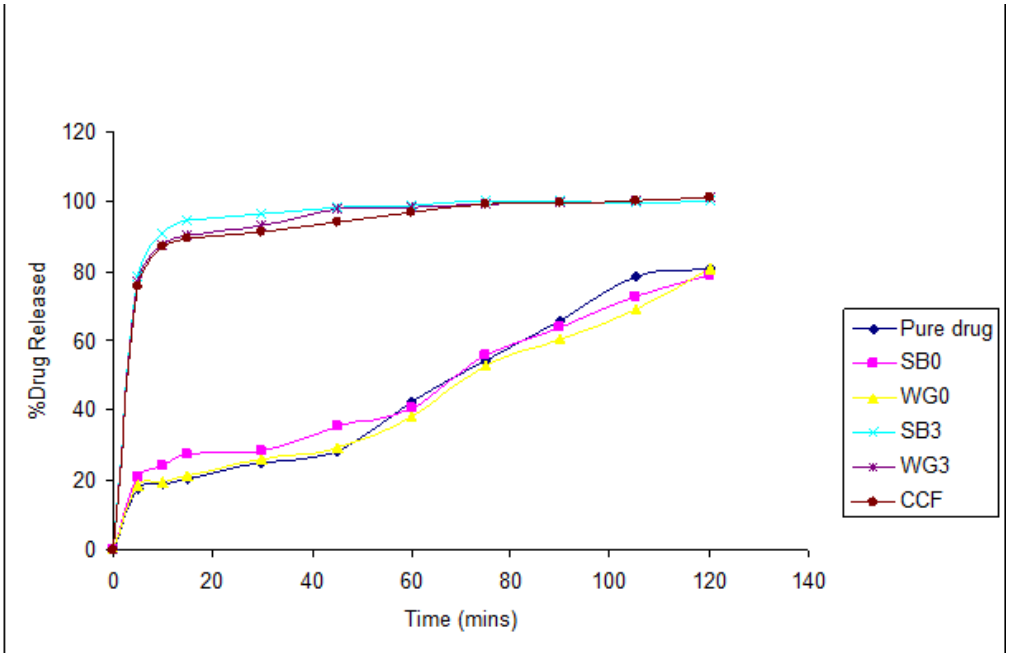

Fig 2: *In vitro* Dissolution data of promising tablet formulations of Irbesartan, Pure drug, Control and Commerial formulation

Formulation Code	D10 (%)	t50% (min)	t70% (min)
Pure drug	19.0	75	105
WG_0	19.6	75	105
WG_3	87.5	<5	5
SB_0	24.0	75	105
SB_3	90.5	<5	5
$_{CCF}$	51.2	10	20

D10 is cumulative percent drug released in 10 min; t50% and t70% are time for 50% and 70% drug release respectively.

Table No.5: Comparative *In Vitro* Dissolution Parameters of Pure Drug, Control, Promising Irbesartan Formulations and Commercial formulation in 0.1N HCl.

CONCLUSION

The work conclusively reveals that Fast dissolving tablet of Irbesartan fulfilling all the requirements can be prepared by simple and cost-effective procedure by Sublimation technique for improving patient compliance, rapid onset of action over formulations prepared using Wet- granulation technique.

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