Development and evaluation of novel antihypertensive orodispersible tablets

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Abstract: Objective of present study was to enhance patient compliance in pediatrics and geriatrics patients of Hypertension. To achieve this target, innovative orodispersible tablets of atenolol and atorvastatin was developed to produce instant action by rapidly disintegrating into oral cavity. Three different techniques like direct compression, effervescent and sublimation methods were used to prepare these tablets (Five batches of tablets by each method) by using two superdisintegrants like Sodium starch glycolate and pregelatinized starch alone and in combination. Pre-formulation studies including rheological analysis (Bulk density, tapped density, Angle of repose, Carr's compressibility index, Hausner's ratio), compatibility studies such as Fourier transform infrared spectrophotometry (FTIR) and Differential scanning colorimetry (DSC), Post–compression and stability studies were also performed. Finally, results were statistically evaluated by the applying one way ANOVA test and mean. It was concluded that the formulation F8 containing Sodium starch glycolate 2% and pregelatinized starch 6% found best regarding disintegration time, wetting volume, wetting time, release studies etc. The order in which drug release was quicker is Pregelatinized starch plus Sodium starch glycolate > Pregelatinized starch > Sodium starch glycolate (primojel). It was concluded that sublimation method was the best among three methods used for orodispersible tablets formulations.

Keywords: Atenolol, atorvastatin, orodispersible, primojel, sublimation.

INTRODUCTION

Recent advancement in the field of pharmaceutical sciences is novel and attractive drug delivery systems (DDS) for pediatrics and geriatrics. Mouth dissolving tablets are innovative dosage form that enhances Patient Compliance (Malke *et al*., 2007). Orodispersibles are used to overcome the problem Dysphagia, is a major hurdle while taking tablets and capsules (Seager, 1998).

Orodispersible tablets, rapidly disintegrate within three minutes before swallowing, having saliva as disintegration medium and show good bioavailability (Bandari *et al*., 2008; Bi *et al*., 1999; Indurwade *et al*., 2002; Manivannan, 2009; Patel and Patel, 2008; Song *et al*., 2004; Wilson *et al*., 1987).

Natural as well as chemically synthetic superdisintegrants are added to hasten the disintegration of the tablets (Marshal, 1987). Direct compression method, effervescent method, sublimation method, mass extrusion method, tablet moulding and Zydis technologies are being currently used for manufacturing of these tablets (Gudas *et al*., 2010; Kalia *et al*., 2009).

Atenolol an antihypertensive moiety, competitive is an antagonists at beta adrenergic receptor sites. Atorvastatin HMG-CoA reductase inhibitor (statin) that lowers plasma cholesterol levels (Bontchev *et al*., 2002).

In the present study orodispersible tablets of Atenolol and Atorvastatin are prepared by using Pregelatinize starch and Primojel. Three techniques are used for their manufacturing i.e. direct compression, sublimation, and effervescent method to prepare these dosage forms. Objective of present innovative preparation is to overcome the side effects associated with frequent tablets and capsules dosage forms.

MATERIALS AND METHODS

Materials

Atenolol, Atorvastatin, Pregelatinized starch, Primojel, Talc, Sodium Bicarbonate, Tartaric acid, Camphor, saccharine, Magnesium stearate and Orange flavor were used. Atenolol and Atorvastatin were obtained as gift samples from Warrick pharmaceuticals, Islamabad, Pakistan. Primojel and saccharine were obtained from Fynk Pharmaceuticals, Islamabad, Pakistan. Pregelatinized starch and Orange flavor were taken from Saffron pharmaceuticals, Faisalabad, Punjab, Pakistan. All the chemicals used were of analytical grade.

Preparation of orodispersible tablets

Three different techniques prepared the orodispersible tablets.

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Direct compression

All the ingredients were weighed and passed through sieve no.60 and mixed for 20 minutes in polythene bags to bring uniformity of powder blend. Weighed ingredients for each tablet were poured into dye of the 19 punches rotary tablet machine. tablet weight was adjusted to 150mg. Machine was operated manually using 7mm flat punches. Compression force was kept 3.2 (Kalia *et al*., 2009).

Sublimation method

Primojel, Pregelatinized starch and lactose in various concentrations along with subliming agent i.e. Camphor were used to develop five formulations (F6-F10) of orodispersible tablets. All the ingredients were weighed and passed through sieve no.60 and mixed for 20min. Powder blend was weighed individually 150mg each time for each tablet and compressed using 7mm flat round punch manually. After compression, these compressed tablets were dried for 5 hours (Suresh *et al*., 2007).

Effervescent method

All the ingredients were sieved through sieve no.60. The sodium bicarbonate and tartaric acid were preheated at 80°C for 2hours to remove any residual or fraction of moisture which may lead to any instability of dosage form.

All the ingredients were mixed geometrically by pouring in polythene bag for 20minutes. Each tablet of 150mg compressed on 19-station tablet rotary machine using7mm flat round punch (Kaushik *et al.*, 2004).

Evaluation of powder blend

Angle of repose, bulk density, tapped density, Carr's compressibility index and hausner's ratio were calculated by using following formulas;

Angle of repose

$$Tan\theta = \frac{h}{r}$$

Powder mixture was poured throughout a funnel that was raised perpendicularly awaiting a cone with maximum height (h). A circle was drawn with lead pencil. Radius (r) of the heap (r) was deliberated (Mahmood *et al*., 2016).

Bulk density

$$Bulk\ density\ (\rho b) = \frac{M}{Vb}$$

M = mass of the powder, Vb = Bulk volume of the powder

Specified quantity (M) of powder blend was poured in measuring cylinder of volume (V). Bulk volume (Vb) was noted (Mahmood *et al*., 2016).

Tapped density

$$Tapped\ density\ (\rho t) = \frac{M}{Vt}$$

M = mass of the powder, Vt = Tapped volume of the powder

Tap density was calculated by tapping filled cylinder for a fixed period at a preset height. Tapped volume (Vt) was noted (Mahmood *et al*., 2016).

Carr's compressibility index

$$Carr's\ Compressibility\ index\ (I) = \frac{Vt - Vb}{Vb}\ x\ 100$$

Vb = bulk volume, VT = tapped volume

If Carr's index is amid 13%-19% it indicates good flow chattels and if more than 21% than it shows poor flow (Mahmood *et al*., 2016).

Hausner's ratio

$$Hausner\ ratio = \frac{\rho t}{\rho b}$$

ρt = tapped density, ρb = bulk density Hausner's ratio less than 1.25 show better flow while more than 1.25 show poor flow (Mahmood *et al*., 2016).

In-vitro evaluation of orodispersible tablets

Tablet hardness

Three tablets were selected arbitrarily from each formulation. Each tablet was placed horizontally and independently between two arms of the Digital hardness tester. After the breakdown of the tablet, hardness was shown digitally in kg/cm^2. Average of three tablets was determined and results were reported (Mahmood *et al*., 2015).

Tablet thickness and diameter

Thickness and diameter were measured also on digital hardness tester. tablet was placed vertically between two arms of the tester. Average of three values was noted (Mahmood *et al*., 2015).

Weight variation test

Twenty tablets were selected haphazardly and weighed alone and their average weight was calculated by adding weight of individual tablet and dividing their sum by their number. Then limit was established by ±7.5%. All the tablets were falling in that limit (Sarfraz *et al*., 2015).

Friability

The mechanical strength of the orodispersible tablets was determined by using Roche Friabilator. Tablets were selected aimlessly from each formulation and their initial weight (Wo) was noted. Friabilator was specified at a speed of 25rpm for 4 minutes. tablets were placed in the drum and allowed to fall from 6 inches for four minutes. After 4 minutes, tablets were removed, dedusted and reweighed (W). Friability was calculated by using following formula (Sarfraz *et al*., 2015).

$$Friability\ (f) = \frac{(1 - Wo)}{W}\ x\ 100$$

Weight loss should not be more than 1%.

Table 1: Composition of Orodispersible tablets

Ingredients (mg)	Direct Compression tablets (F1-F5)					Sublimation tablets (F6-F10)					Effervescent tablets(F11-F15)				
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Atenolol	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Atorvastatin Calcium	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Pregelatinized Starch	12	-	9	6	3	12	-	9	6	3	12	-	9	9	3
Primojel	-	12	3	6	9	-	12	3	6	9	-	12	3	9	9
Mg-Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Lactose	74	74	74	74	74	64	64	64	64	64	44	44	44	44	44
Orange Flavour	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Saccharine Sodium	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Camphor	_	_	_	_	_	10	10	10	10	10	_	_	_	_	_
$NaHCO_3$	_	_	_	_	_	_	_	_	_	_	15	15	15	15	15
Tartaric Acid	_	_	_	_	_	_	_	_	_	_	15	15	15	15	15
Total Weight	150mg					150mg					150mg				

Table 2: Flow properties of bulk powder used in orodispersible tablets.

Code	Bulk Density (g/mL)	Tapped Density (g/mL)	Angle of Repose (□)	Hausner's Ratio	Carr's Index (%)
F1	0.607	0.739	23.6	1.21	17.85
F2	0.630	0.744	20.8	1.18	15.25
F3	0.610	0.740	24.9	1.21	17.12
F4	0.599	0.711	23.7	1.18	16.07
F5	0.612	0.725	24.2	1.18	16.25
F6	0.601	0.720	23.8	1.19	16.80
F7	0.618	0.741	22.6	1.19	17.95
F8	0.613	0.719	21.9	1.17	15.19
F9	0.621	0.733	23.5	1.18	15.46
F10	0.639	0.729	24.4	1.14	14.90
F11	0.630	0.736	22.7	1.16	15.13
F12	0.628	0.727	20.4	1.15	16.01
F13	0.634	0.731	22.6	1.15	15.92
F14	0.640	0.738	23.3	1.15	15.19
F15	0.615	0.728	24.9	1.18	16.78

All values are average of three determinations.

Tablet disintegration

Complete breakdown time of an orodispersible tablet was determined by using disintegration apparatus. Apparatus was washed and six tablets were placed separately in six tubes of the apparatus. Phosphate buffer (pH= 6.8) was used as disintegration medium. Temperature was maintained throughout the procedure at 37°C±2°C. Complete disintegration time was noted that was within the official limits (Sarfraz *et al*., 2015).

Dissolution test

Dissolution studies were performed in USP Type II for all fictional formulations. The apparatus was set at 50 rpm in 900ml of dissolution media (Phosphate Buffer of pH 6.8). The temperature of the media was reserved at 37°C±2°C. Sample of 5ml was drawn from each basket with equal replacement of dissolution media. The samples were filtered, diluted, and assayed to know absorbance of the samples (Sarfraz *et al*., 2015).

Modified disintegration test

In this method, a Petri dish with internal diameter of 10cm was used. 10 ml of phosphate buffer was used as disintegration media. A solo tablet was selected from each fabricated formulation and kept in the center of the Petri dish. The disintegration time was noted (Sameer *et al*., 2009).

Content uniformity test

Drug content of each formulation was determined and found to be between 95%-105% which was within the legal limits. Equal quantities of powder and standards were taken and assayed at respective wavelengths after suitable dilutions and filtration (Bala *et al*., 2012).

pH of the orodispersible tablet solution

Orodispersible tablet was dissolved in 200 ml distilled water and checked pH by using pH meter.

Wetting volume

Volume of the phosphate buffer pH 6.8 was used as wetting solution. A petridish of internal diameter 10cm was taken with tissue paper. Wetting media was taken in 10ml graduated pipette. Volume of buffer solution used for complete wetting was noted.

Table 3 *In-vitro* Evaluation of Orodispersible Tablets

Code	Weight Variation (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability* (%)	Disintegration*Time (s)	Wetting* Time (s)	Wetting* volume (ml)	Dispersion* time (Sec)	pH	Water* absorption ratio
F1	148.32	3.5	2.52	0.715±0.01	38±1.00	61±1.00	19±0.58	44±1.00	7.3	1.20±0.05
F2	147.51	3.7	2.54	0.674±0.01	55±1.00	88±1.53	23±1.00	56±1.15	6.9	0.90±0.10
F3	148.86	3.6	2.61	0.451±0.00	34±1.00	45±1.00	15±1.53	38±1.00	7.2	1.30±0.05
F4	151.21	3.4	2.98	0.842±0.02	42±1.53	66±1.53	22±1.00	48±1.53	7.1	1.15±0.04
F5	150.91	3.4	2.75	0.669±0.01	50±1.00	73±1.00	21±0.58	53±1.00	6.8	1.00±0.20
F6	148.66	3.3	2.86	0.712±0.00	31±0.58	55±1.00	16±0.58	40±1.73	7.1	1.30±0.10
F7	148.17	3.6	2.41	0.561±0.00	50±1.15	75±1.00	20±1.15	50±0.58	7	1.00±0.10
F8	148.54	3.2	2.53	0.862±0.00	28±1.00	37±1.00	12±0.58	29±1.15	7.2	1.50±0.05
F9	151.56	3.1	2.65	0.547±0.00	40±1.00	60±1.00	19±0.58	43±1.15	7.1	1.20±0.06
F10	147.85	3.3	3.01	0.712±0.00	46±0.58	68±1.00	20±1.15	49±1.15	7.2	1.15±0.03
F11	149.54	3.2	2.89	0.564±0.00	36±1.15	56±1.15	17±1.15	40±1.73	7	1.20±0.04
F12	151.35	3.3	2.78	0.412±0.00	50±2.31	79±1.15	21±1.15	54±0.58	6.9	1.00±0.11
F13	152.21	3.3	2.56	0.731±0.00	32±2.31	39±1.15	15±1.15	33±1.73	7	1.40±0.02
F14	151.55	3.2	2.64	0.841±0.00	39±0.58	64±1.15	21±1.73	45±0.58	7.4	1.10±0.28
F15	152.65	3.1	2.55	0.654±0.00	43±1.15	70±1.15	18±2.31	50±1.73	7.2	1.00±0.12

*n = 3 ± S.D. (Standard deviation)

Water absorption ratio

Amount of water absorbed by the tablet was calculated by placing the tablet in petridish centrally. A tissue paper folded twice was placed in the petridish. Tablet was weighed before wetting and reweighed after complete wetting. Water absorption ratio was calculated by using following formula (Gohel *et al*., 2005).

$$R = \frac{Wa - Wb}{Wb} x\ 100$$

Wa = Weight of the tablet after wetting, Wb = Weight of tablet before Wetting.

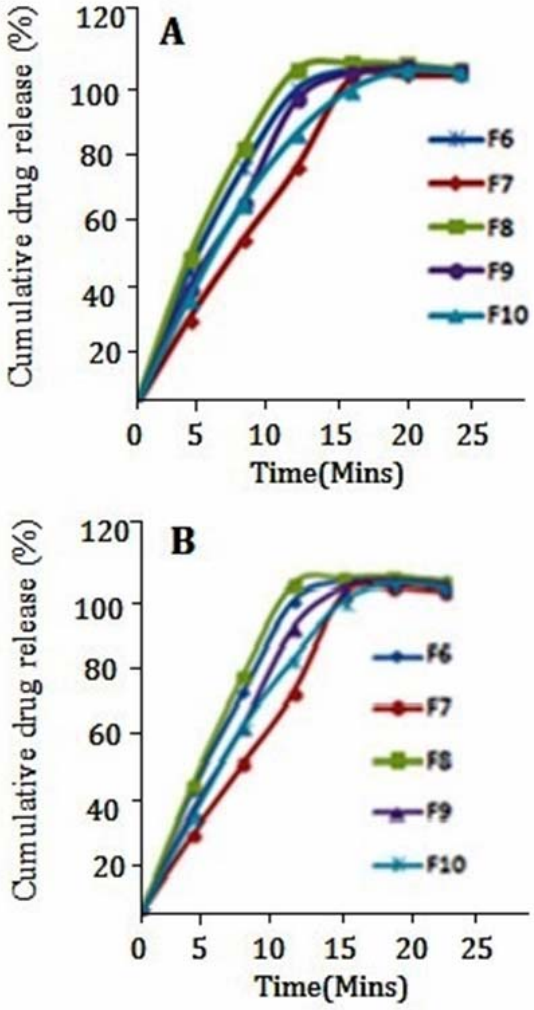


Fig. 1: Drug release profile of best formulation (F8) at pH 6.8 (a) Atenolol (b) Atorvastatin Calcium.

FTIR studies

Spectra were recorded for pure drugs (Atenolol and Atorvastatin) and superdisintegrants (Primojel, Pregelatinized starch, Kyron T and Crosscaramellose sodium). Pellets were prepared in KBr press (2 mg sample in 200 mg KBr) under a hydraulic pressure of 150kg/cm^2. Scanning range was 4,000-400cm^{-1} and the resolution was 2cm^{-1}. Compatibility b/w pure drugs and superdisintegrants were checked and FTIR (IR Prestage 21 Shimadzu)-Spectra was taken (Sarfraz *et al*., 2016).

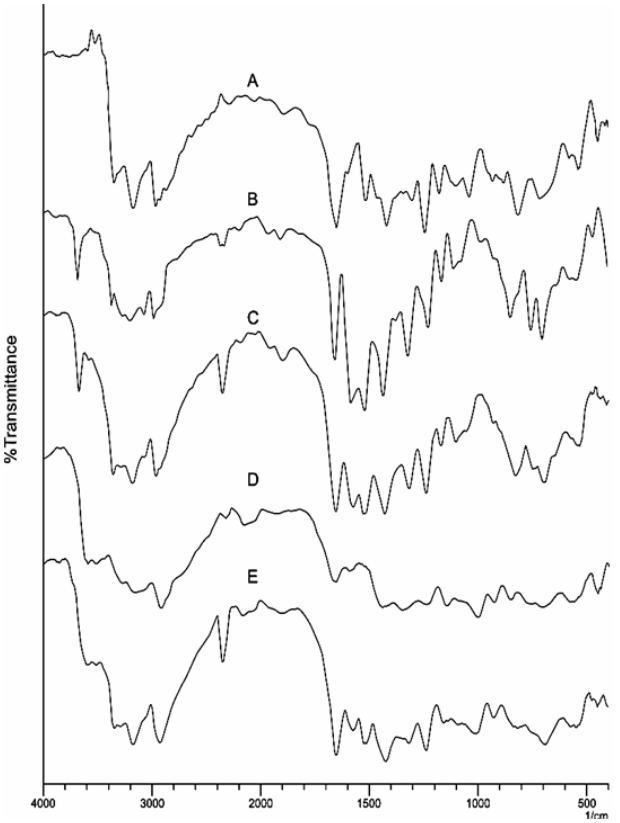


Fig. 2: FTIR spectra of A: Atenolol, B: Atorvastatin, C: Primojel, D: Pregelatinized starch E: mixture of Atenolol, atorvastatin, Pregelatinized starch and Primojel.

DSC studies

DSC analysis was conducted to analyze any possible drug-drug and drug superdisintegrants interaction. Thermal curves of pure components (Drugs & superdisintegrants) and their mixtures were recorded. DSC analysis of pure drugs, and superdisintegrants were carried out using SDT. Q 600 Thermal Analyzer USA to evaluate any possible drug- superdisintegrants interaction. Superdisintegrants and drugs (atenolol and atorvastatin) were triturated separately to get a finely divided powder and heated in sealed aluminum pans at a rate of 10^{o}C/min from 0 to 176^{o}C temperature range under a nitrogen flow of 40ml/min. Reproducibility was checked by running the sample in triplicate (Sarfraz *et al*., 2016).

STATISTICAL ANALYSIS

All the results were evaluated statistically by using one way ANOVA. Mean of results were also determined.

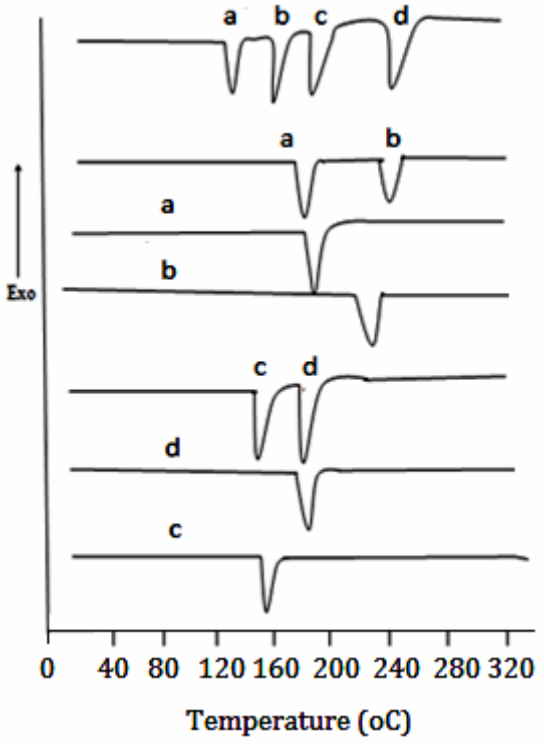
Stability studies

Stability studies were done for a period of six months. All the physical and *in vitro* tests were performed according

to ICH guidelines and no significant changes were observed. Study was performed under following temperature and humidity conditions 40±1˚C, 50±1˚C, 37±1˚C and RH 75%±5%.

RESULTS

Bulk density of 15 formulations was found in the range of 0.599 to o.640 g/ml and tapped density 0.711 to 0.744 g/ml. Angle of Repose, Hausner's Ratio and Carr's Index values were present in the range of 20.4 to 24.9, 1.14 to 1.21 and 14.90 to 17.95, respectively. These results of powder blend were within specified limits (table 2). Results of weight variation, hardness, thickness, and friability were present within the pharmacopoeial limits (table 3). Weight variation limits for 150 mg tablets is up to ±7.5% (138.75 to 161.25 mg). Overall 15 formulations had weight between 147.51 to 152.65mg. Friability results of overall 15 formulations were up to 0.862% which was below than specified limits(less than 1%). Disintegration time (28 to 55 sec), wetting time (37 to 88 sec) and dispersion time (29 to 56 sec) were measured for each individual formulation.



Tablets should disintegrate completely in oral cavity up to 3 minutes. Results had clearly shown that disintegration time was even less than 1 minute. Dispersion time is also less than 1 minute. These all parameters were lying well in the specified range as shown in table 3.

Results had shown that the release of Atenolol was in the range of 97% to 102% for 15 formulations in 12 minutes (fig.1 a,b,c). Atorvastatin release was in the range of 96% to 100.5% (Fg.1 d,e,f). Atenolol release is more as compared to Atorvastatin. Wetting volume was 12 to 23 ml. pH of tablets solution was approximately near to neutral, Water absorption ratio was up to 1.50 it revealed that tablets had good ability to absorb water.

FTIR results had shown that there were no interactions among the drugs as well as drugs and excipients and between the excipients. DSC study also proved that dugs and excipients had no interactions with each other. Stability studies of (6 months) at accelerated conditions of temperature and humidity had shown that tablets remained stable for prescribed time period.

DISCUSSION

Rheological study proved good flow properties of powder and it meets the required criteria for excellent flow. Angle of repose below 30 indicated that powder had good flow properties and our results lie between 20.4 to 24.9. Higher values of angle of repose favor poor flow due to aggregates formation. Value of Carr's index between 13% to 19% is considered acceptable and our results lie between 14.90% to 17.95%. Powder blend of micrometric size range usually offer good flow due to presence of least attractive forces between the individual particles. These results justified that powder blend had good flow. Hausner's ratio below 1.25 indicates that powder had better flow and results were between1.14 to 1.21. Overall results of all parameters of rheological properties were well within the specified limits and these have confirmed better flow ability of the powder blend.

Weight variation results showed that tablets were of proper weight and size and were within the developed limits. There was consistency among the prepared tablets and minimum batch to batch variation was detected.

Tablets prepared by direct compression method had more hardness as compared to both other methods. Proper hardness indicates that tablets can bear stress and remain stable during storage, handling, and transportation. tablets prepared by direct compression method offered more hardness values. Higher values of hardness promote tablet density due to reduction in porous spaces among powder bend. In sublimation method camphor was used as subliming agent which induces more porosity after evaporation and tablets were little bit less hard. tablets containing Primojel as superdisintegrant had more hardness than tablets containing pregelatinized starch. It is due to more porous nature of Pregelatinized starch. Overall results of hardness and thickness indicated that they were present within prescribed limits of ODT's. Tablets had good mechanical strength as friability was less than 0.9%. Results of ANOVA between the groups had shown that *p*-value was 0.090. Results within groups were highly significant. Friability of tablets had not

clearly affected by the method of preparation but concentration of superdisintegrant effects the tablet friability. Similar results were found in another study conducted by (Mahmood *et al*., 2015).

All the formulations had drug content uniformity within the range of 96% to 100.5% indicating uniform and proper distribution of drugs in the prepared tablets. Wetting time is the indication of hydrophobicity of the ingredients. Lesser the wetting time faster will be the disintegration (Bandari *et al*., 2008). All the formulations had wetting time less than 90 seconds. It is less for tablets containing pregelatinized starch as compared to tablets having same quantity of sodium starch glycolate. It is due to rapid disintegrating nature of pregelatinized starch. Results showed that tablets containing both sodium starch glycolate and Pregelatinized starch in the ratio of 1:3 had wetting time less than formulations containing sodium starch glycolate and Pregelatinized starch alone. F8 formulation had wetting time 38 seconds which is lowest for all 15 formulations containing sodium starch glycolate and Pregelatinized starch as superdisintegrant. It was also observed that tablets prepared by sublimation method had less wetting time as compared to tablets prepared by effervescent and direct compression method. It is due to the rapid water absorbing nature of camphor and porosity created by camphor also promotes fast disintegration of prepared sublimed tablets. Similar outcomes were also seen in our previous study conducted by (Sarfraz *et al*., 2015).

Results of one way ANOVA had shown that *p*-value for wetting time between the groups was 0.072. Statistically there was very little effect of method of preparation on tablet wetting but our data had shown that there was difference in drug wetting time in tablets of various groups that were prepared by different methods. Wetting time within groups was highly significant indicating that wetting of tablets greatly affected by the concentration of superdisintegrants.

Disintegration time for ODTs is generally below 1 minute and time that patient can experience is 5 to 30 seconds (Bandari *et al*., 2008). Disintegration time for all the formulations was less than 1 minute which is very acceptable for ODTs. Like wetting time, it is also very less for tablets containing pregelatinized starch. It was also observed that tablets prepared by sublimation method had low disintegration time as compared to other methods. The disintegration time for pregelatinized starch containing tablets were less than tablets containing sodium starch glycolate. It was even less for tablets having both pregelatinized starch and sodium starch glycolate in ratio of 3:1. Method of preparation also affects disintegration. F8 formulation prepared by sublimation method had lowest disintegration time of all 15 formulations. Results of both wetting time and disintegration time studies agreed indicating that all formulations would disintegrate in oral cavity within specified time. Results of one way ANOVA had shown that p-value for disintegration time between the groups was 0.064. It indicated that results were insignificant and there was very little effect of method of preparation on tablet disintegration statistically but our data had shown that there was difference in drug disintegration time in tablets which were prepared by different methods. Disintegration time within groups was highly significant which indicates that concentration of superdisintegrants greatly affect the tablet disintegration.

Formulation (F8) containing 6% of pregelatinized starch and 2% sodium starch glycolate prepared by sublimation method also had less wetting volume. Statistically the results of wetting volume between the groups were insignificant and within the groups were highly significant. It represented that wetting volume for tablets depend upon the method of preparation and concentration of superdisintegrants.

Formulation F8 containing pregelatinized starch and primojel had shown less dispersion time 29 seconds when compared with formulations containing primojel and pregelatinized starch as superdisintegrant. Order in which formulations were disintegrate quickly was pregelatinized starch plus sodium starch glycolate > pregelatinized starch > sodium starch glycolate.

Results of ANOVA between the groups had shown that *p*-value was 0.055. *In vitro* dispersion time of tablets was significantly affected due to the concentrations of superdisintegrant and method of preparation had less effect on tablet dispersion time.

All the formulations had good water absorption ratio than original weight. Formulation F8 containing 6% pregelatinized starch and 2% sodium starch glycolate prepared by sublimation method showed more water absorption ratio as compared with formulations containing same composition but prepared by direct compression and effervescent method.

Combined use of pregelatinized starch and primojel showed better results as compared to their single use (Bhardwaj *et al*., 2010).

Results of one way ANOVA had shown that p-value for water absorption ratio between the groups was 0.053 there was little effect of method of preparation on tablet disintegration statistically but our data had shown that there is difference in drug water Absorption Ratio. Water Absorption Ratio within groups was significant which indicated that concentration of superdisintegrants affected the tablet disintegration.

Cumulative % of drug release was measured up to 12 minutes and with the increase in the concentration of superdisintegrants maximum up to 8%. When superdisintegrants concentration was further increased then tablets friability, hardness etc were affected. Pregelatinized starch (6%) and primojel (2%) containing tablet (F8) had shown maximum release of drug 99.5% in 12 minutes. Formulations F3, F8 and F13 all three had 6% of Pregelatinized starch but F8 had shown maximum drug release. It was seen that drug release was also affected by method of preparation. F8 tablet was prepared by Sublimation method. F8 tablet contained camphor which created more porous structure and more water was observed. Thus, more rapidly drug was released when compared with other two methods (Bhardwaj *et al*., 2010). Release of Atenolol was in the range of 97% to 99.5% for fifteen formulations in 12 minutes. Atorvastatin release was in the range of 96% to 99%. These results had shown that Atenolol release was more as compared to Atorvastatin.

FTIR (fig. 2) spectra of pure Atorvastatin Calcium showed characteristic peaks at 2955.15 cm^{-1}(C-N - stretching), 3059.15 cm^{-1} (C-H - stretching), 1313.56 cm^{-1} (C-HO - stretching alcoholic group), 1564.97 cm^{-1} (C=O - stretching amidic group), 3403.27 cm^{-1} (N-H - stretching), 1656.97 cm^{-1} (C=C - bending), 751.62 $cm^{-1}$and 696.95 cm^{-1} (C-F - stretching), 1104.39 cm^{-1} (O-H - bending). It might be the possibility of intermolecular hydrogen bonding between adjacent Atorvastatin Calcium molecules. Spectrum of pure Atorvastatin Calcium was like the spectra obtained by the addition of superdisintegrants (Lakshmi *et al*., 2011).

IR spectrum of atenolol was characterized by the presence of absorptive band (-COOH group) at 1651 cm^{-1}**.** IR spectrum of pure drug (Atenolol) was recorded with Atorvastatin Calcium and superdisintegrants. Same absorption spectra of atenolol were obtained. These results revealed that no considerable changes in the IR peaks of Atorvastatin Calcium, when mixed with drug Atenolol and with polymeric superdisintegrants like Kyron T_{134}, Pregelatinized starch, Crosscaramellose sodium and primojel. These observations indicated the compatibility of Atorvastatin Calcium and Atenolol with each other and with superdisintegrants (Jagdale *et al*., 2010).

DSC studies (fig. 3) of drugs molecules and superdisintegrants were carried out alone as well as in combination. Characteristic peaks of alone drugs and with excipients were compared. This study also confirms that there was no interaction among drugs and excipients. Presence of endothermic peaks in the fabricated ODT's confirmed the successful incorporation of drugs.

In case of atenolol initially flat or smooth profile was observed but when it entered in to its melting range 154^{o}C, sharp endothermic peak was observed as shown in fig. 3. Similarly in case of atorvastatin calcium initially flat or smooth profile was observed but when it entered its melting range 176^{o}C, sharp endothermic peak was observed. DSC thermograms of drugs (atenolol and atorvastatin) were taken with two superdisintegrants **(**primojel and pregelatinized starch). Characteristics thermograms of alone drugs and with superdisintegrants were compared. Results revealed no considerable changes in the thermograms of dugs alone and in combination with superdisintegrants. These observations indicated the compatibility of Atorvastatin Calcium and Atenolol with each other as well as with superdisintegrants (Tayade and Kale, 2004). Stability studies indicated that there were no significant variations occurred in drug content and *in vitro* dispersion time at the end of 6 months.

CONCLUSION

Rheological properties of powder blend existed well within given limits which demonstrated that powder had good flow. DSC and FTIR spectroscopic studies had presented that drugs with each other as well as with excipients were free from interactions. This study concludes that Pregelatinized starch is the best superdisintegrant. Sublimation method is better than other methods and effervescent is better than direct compression method used to prepare orodispersible tablets.

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