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FORMULATION AND IN-VITRO EVALUATION OF NOVEL ATORVASTATIN - AMLODIPINE ORODISPERSIBLE TABLETS

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ABSTRACT

The purpose of study was to fabricate rapid acting tablets for traveling, unconscious and unresponsive hypertensive patients thereby improving patient compliance, decreasing cost of the treatment and number of pills. Novel antihypertensive orodispersible tablets (ODT's) of amlodipine and atorvastatin were prepared by direct compression and sublimation technique. Kyron T_{134} and Crosscaramellose sodium were used as superdisintegrant. Ten formulations (F1-F10) were prepared by varying superdisintegrants concentration to optimize the best formulation. Pre-compression studies like Bulk density, Tapped density, Angle of repose, Carr's compressibility index, Hausner's ratio to note flow properties of powder and compatibility studies such as Fourier Transform Infrared Red spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were performed to check any interaction between drugs and superdisintegrants. Then after flow and compressibility studies powder was compressed into ODT's. Various features such as hardness, thickness, diameter, weight variation, friability, disintegration time, dissolution studies, wetting time, wetting volume, water absorption ratio, modified disintegration time, uniformity of contents and stability of formulated ODT's were

evaluated. All the results were within the acceptable Pharmacopoeial limits and were evaluated statistically by using one way ANOVA test. From the results it was observed that F8 formulation prepared by sublimation method containing both Kyron T_{134} 12 mg and Crosscaramellose sodium 4 mg were most appropriate formulation from every aspect of the study conducted. Thus it was concluded that sublimation method is better as compared to direct compression method for the preparation of ODT's and superdisintegrants show promising effects in combination than when used alone.

Keywords: Orodispersible Tablets, Kyron T_{134}, Crosscaramellose Sodium, Sublimation, Direct Compression

INTRODUCTION

The modern era belongs to the development of new and new dosage forms that are according to the needs of patients. Efforts are being made to improve safety, efficacy and bioavailability with minimal dosing frequency and adverse effects in order to enhance patient compliance **[1]**. Oral cavity have shown three different types of mucosal layers i.e. masticator mucosa, lining mucosa and specialized mucosa having surface area of 100 cm^2 within the oral cavity **[2]**. Problems like dysphasia, bitter taste, nausea and vomiting, diarrhea, lack of access to water etc have been eliminated by the development of new drug delivery system i.e. orodispersible tablets. The tablets disperse instantaneously into absorbable form within 15 sec-3 mins after their placement in the oral cavity with the aid of saliva **[3]**. Their importance has markedly increased due to the inclusion of name "orodispersible tablet" in European pharmacopoeia as a tablet that disperses instantaneously in oral cavity before swallowing **[4]**. Atorvastatin is a synthetic competitive inhibitor of 3-hydroxy- 3-methylglutaryl coenzyme A (HMG-CoA) reductase, that inhibits cholesterol synthesis by the conversion of HMG-CoA to mevalonate thereby resulting in decrease in heart related diseases and death cases. It has less oral bioavailability 12 – 14% and enhance metabolism in liver **[5]**. Amlodipine besylate is 2-[(2-aminoethoxy)-methyl]-4- 2-chlorophenyl), 1, 4-dihydro-6-methyl-3, 5-pyridine dicarboxylic acid, and 3-ethyl-5-methyl ester. It is slowly and completely bioavailable within 6-12hrs. A large number of superdisintegrants are used in fabrication of orodispersible tablets. These include cross caramellose sodium, crospovidone, sodium

starch glycolate, chitosan, indion 414 etc. Most frequently used superdisintegrants are crosscaramellose sodium, crospovidone, sodium starch glycolate and kyron T_{134} **[6, 7]**. ODT's were prepared by various methods like direct compression, sublimation method, effervescent method etc. Each method has its own advantages and disadvantages but most frequently direct compression is used in preparing orodispersible tablets **[8]**.

MATERIALS AND METHODS

Materials

Amlodipine and kyron-T_{134} were received as generous gift sample from Wilson pharmaceuticals, Islamabad, Pakistan. Saccharine was obtained from Fynk pharmaceuticals, Islamabad, Pakistan. Crosscaramellose sodium, Atorvastatin and Orange flavor were taken from Saffron pharmaceuticals Faisalabad, Punjab, Pakistan. All the chemicals were of high purity standard.

Methods

Ten formulations containing kyron-T_{134} and crosscaramellose sodium alone, in combination and in different concentrations were prepared by direct compression (F1 – F5) and sublimation methods (F6 – F10). All ingredients were weighed and sieved through sieve no.60 and grinded in pestle mortar to bring fineness in the powder **[9]**. In both methods all ingredients of ODT's were mixed in geometrical order and compressed by using 8 mm round flat punches on 19 station rotary tablet machine **[10]**. In Sublimation method, Camphor was added subliming agent. After sieving and mixing, the blend was compressed into 150 mg tablets **(Table 1)**. Compressed tablets were sublimed in hot air oven for 6 hours at 60 $\pm$1˚C **[11]**. A batch of 100 tablets was prepared by each method for further characterization.

Standard deviation (SD), averages and one way ANOVA were used to interpret the results.

Characterization

Pre- Compression Studies

Angle of Repose

Angle of repose was determined by funnel method by addition of powder blend to a vertically placed funnel until maximum cone height (H) was obtained. Radius of heap (R) was measured and (Θ) angle of repose was calculated as **[12]**;

$\Theta = \tan^{-1} (H/R)$

Bulk Density

Drug and excipients mixture was sieved and then placed in the graduated cylinder .The volume and weight of powder was determined **[12]**;

Bulk density= weight of powder/volume of powder

Tapped Density

The tapped density was calculated by tapping the cylinder having pre-weighed powder and then tapped it for 100 tappings **[12]**;

$$Dt = W/Vb$$

Dt = Tapped density, W = wt of powder, Vb = vol. of powder

Carr's Index

The flowability of powder was measured by compressibility index i.e. a property with which material flowed easily **[12]**;

$$\text{Carr's index} = I = (Vb-Vt) \times 100 / Vb$$

Hausner's Ratio

It is an indirect method for measuring ease of powder flow **[12]**;

$$\text{Hausner's ratio} = Dt/Db$$

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 **[13]**.

DSC Studies

The DSC analysis of pure drugs (amlodipine and atorvastatin), superdisintegrants (Kyron T_{134} and crosscaramellose sodium) and drug-superdisintegrants was conducted on SDT. Q600 TA USA to evaluate any possible interactions. Sample was triturated to make them fine in size and then heated in sealed aluminium pan at a heating rate of 10ºC/min from 0 to 226ºC. The nitrogen flow was 40ml/min. Reproducibility was checked by running sample in triplicate **[13]**.

Post Compression Studies Tablet; Hardness, Thickness, Diameter and Weight Variation

Hardness (Kg/cm^2), thickness and diameter of tablets were determined to check the stability of tablets during traveling and manufacturing stresses on digital hardness tester (Pharma Test Germany). For weight variation electrical weighing balance (Shimadzu, Japan) was used **[12]**.

Friability

Roche friabilator was used to calculate the friability of tablets using (Pharma Test Germany). Twenty tablets were weighed on electronic weighing balance (Shimadzu, Japan) and their weight was noted as initial weight. Tablets were placed in the drum of friabilator. The friabilator was operated at a speed of 25 rpm for 4 minutes. After 4 minutes tablets were re-weighed in order to determine final weight of the tablets **[12]**.

Friability (f) = (1- Wo/W) X 100 ------- (6)

Wo = Weight of tablets before the test

W = Weight of tablets after the test

Tablet Disintegration

One tablet was placed in each tube of disintegration apparatus (Pharma Test Germany). Buffer solution of pH 6.8 was used for disintegration and temperature was maintained at 37°C ± 2°C. The time required for complete disintegration of the tablets was noted **[14, 15]**.

In Vitro Drug Release

Dissolution studies were performed in phosphate buffer of pH 6.8 using USP type-2 apparatus (Pharma Test Germany) with a speed of 50 rpm at 37°C. Samples were taken at predetermined regular intervals of 30 seconds until complete dissolution occurred. The amount of the sample withdrawn was replaced by the freshly prepared phosphate buffer solution **[16]**.

Wetting Volume

This test was used to determine the volume of the Buffer used for complete wetting of the orodispersible tablet. Tablet was placed in a petri dish. 5 ml buffer solution was taken in a pipette and placed drop wise on to the tablet to note wetting volume of tablet **[15]**.

Water Absorption Ratio

A Petri dish with inner diameter of 6.5 cm and having 6 ml water in it was used for this test. A tissue paper folded twice was put in the Petri dish. A pre-weighed tablet was positioned in it, after complete wetting the tablet was re-weighed **[17]**

$$R = [Wa – Wb / Wb] \times 100$$

Wa = Weight of the tablet before wetting

Wb = Weight of tablet after Wetting

Content Uniformity Test

The drug contents of each formulation was determined and found to be between 97%-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 **[7]**.

Stability Studies

Tablets were subjected for stability studies for a period of six months according to international conference on harmonization (ICH) guidelines under following conditions of temperature and humidity 40 ± 1˚C, 50 ± 1˚C, 37 ± 1˚C and RH 75% ± 5% **[18]**.

RESULTS AND DISCUSSION

Before compressing, powder blend was first assessed for rheological properties **Table 2**. 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 ODT's. The weight of tablets was present between 148.60 to 150.50 mg. This indicates that tablets have no weight variation. Friability of all 10 formulations was less than 1% which indicates that tablets had good mechanical strength to bear any sort of stress

during transport and storage. One way ANOVA was used to evaluate results statistically. p-value was 0.039 which indicate that results were significant. It means that friability was significantly affected by the concentration of superdisintegrants and method of preparation. Disintegration time (30 to 58 sec), wetting time (40 to 89 sec) and dispersion time (32 to 60 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 F8 formulation containing both kyron-T_{134} 12 mg and crosscaramellose sodium 4 mg in combination. p-value for these parameters was less than 0.05 which indicates that results were significant. It suggests that disintegration time, wetting time and dispersion time were affected by nature of superdisintegrant and method of preparation. Wetting volume was also less for F8 formulation that was prepared by sublimation method **Table 4**. Statistically, results of wetting volume between the groups were significant and within the groups were highly significant. It represent that wetting volume for tablets was depend upon the method of preparation and concentration of superdisintegrants. In vitro dispersion test was 32 sec for F8 formulation which was lowest among all 10 formulations. The order in which formulations were disintegrate quickly is kyron T_{134} plus crosscaramellose sodium > kyron T_{134} > crosscaramellose sodium. Statistically by one way ANOVA results of in vitro dispersion were significant between the groups. 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 therefore faster disintegration **Table 4**. This disintegration ultimately affect dissolution rate of tablets. It was more for the formulations containing kyron T_{134} as superdisintegrant than crosscaramellose sodium. But it was even more for F8 formulation having both kyron T_{134} and crosscaramellose sodium in the ratio of 3:1. Few other formulations also have both these superdisintegrants but concentration of kyron T_{134} was less than F8 that's why their water absorption ratio was less than F8. The results of one way ANOVA had shown that water absorption ratio within groups were significant which indicates that concentration of superdisintegrants affect the tablet disintegration. The drug release studies were performed up to 16 minutes at 228nm and

269nm for atorvastatin and amlodipine respectively using UV- visible spectrophotometer after appropriate dilution and filtration. Drug release was rapid for F8 formulation that was 99% for amlodipine and 96% for atorvastatin within 16 min. Three best formulations were chosen for stability studies. No significant changes were occurred in various parameters at the end of six months when stability studies were performed under zone 4 according to ICH (International Conference on Harmonization) guidelines.

CONCLUSION

Orodispersible tablets prepared were according to the required specifications. There were no interactions between the drugs and superdisintegrants proved by FTIR and DSC studies. By evaluating all the results it was concluded that kyron T_{134} has better disintegration nature than crosscaramellose sodium when used alone and their combination results in quick disintegration. Sublimation method is more suitable for ODT's than direct compression method.

ACKNOWLEDGMENT

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Table 1: Composition of Orodispersible Tablets

Ingredients (mg)	Direct Compression (F1-F5)					Sublimation (F6-F10)				
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Amlodipine	10	10	10	10	10	10	10	10	10	10
Atorvastatin	10	10	10	10	10	10	10	10	10	10
Kyron-T_{134}	16	-	12	08	04	16	-	12	08	04
Cross caramellose Sodium	-	16	04	08	12	-	16	04	08	12
Mg-Stearate	4	4	4	4	4	4	4	4	4	4
Talc	6	6	6	6	6	6	6	6	6	6
Lactose	95	95	95	95	95	85	85	85	85	85
Orange Flavor	5	5	5	5	5	5	5	5	5	5
Saccharine Sodium	4	4	4	4	4	4	4	4	4	4
Camphor	_	_	_	_	_	10	10	10	10	10
Total Weight	150mg					150mg				

Table 2: Results of Bulk Density, Tapped Density, Angle of Repose, Hausner's Ratio and Carr's Index

Code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (Ɵ)	Hausner's ratio	Carr's index %
F1	0.625	0.737	24.6	1.17	15.90
F2	0.620	0.725	23.3	1.16	15.50
F3	0.610	0.717	24.8	1.17	16.18
F4	0.635	0.737	24.5	1.16	16.23
F5	0.619	0.731	23.7	1.18	15.20
F6	0.630	0.746	25.2	1.18	14.18
F7	0.625	0.740	26.4	1.18	15.95
F8	0.630	0.737	24.8	1.16	15.76
F9	0.620	0.728	25.6	1.17	15.10
F10	0.625	0.732	25.2	1.17	17.40

Table 3: Results of Weight Variation, Hardness, Thickness, Friability, Disintegration Time and Wetting Time

No	Wt. variation (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability* (%)	Disintegration* Time (Sec)	Wetting* Time (Sec)
F1	150.40	3.3	2.76	0.678±0.02	40±1.25	66±1.50
F2	149.00	3.2	2.64	0.576±0.01	58±2.25	89±2.25
F3	150.50	3.4	2.82	0.628±0.02	35±2.60	45±1.50
F4	149.90	3.3	2.79	0.548±0.00	50±2.50	74±1.50
F5	150.80	3.2	2.81	0.538±0.02	54±1.50	83±1.50
F6	148.60	3.3	2.76	0.599±0.00	40±1.25	64±2.50
F7	148.80	3.4	2.92	0.576±0.01	50±2.00	82±150
F8	148.90	3.6	2.60	0.558±0.01	30±1.50	40±1.30
F9	149.50	3.3	2.80	0.643±0.02	45±1.50	69±1.50
F10	150.50	3.4	2.76	0.645±0.01	47±1.30	76±2.00

***Average of three determinations; Standard deviation (SD)**

Table 4: Results of Wetting Volume, Dispersion Time, pH and Water Absorption Ratio

Formulation	Wetting* volume (ml)	Dispersion* time (Sec)	pH of Tablet Sol	Water* absorption ratio
F1	22±1.15	47±1.73	7.1	1.35±0.01
F2	30±1.73	58±1.15	6.8	1.10±0.02
F3	20±1.15	44±1.15	7.0	1.40±0.02
F4	27±0.58	57±0.58	6.9	1.25±0.01
F5	24±0.58	60±1.15	7.0	1.15±0.04
F6	20±1.73	40±1.73	7.0	1.30±0.06
F7	23±0.58	53±1.15	6.9	1.20±0.08
F8	14±1.15	32±2.31	6.8	1.60±0.06
F9	22±0.58	46±0.58	7.2	1.35±0.02
F10	27±0.58	54±1.73	6.9	1.25±0.04

***Average of three determinations; Standard deviation (SD)**

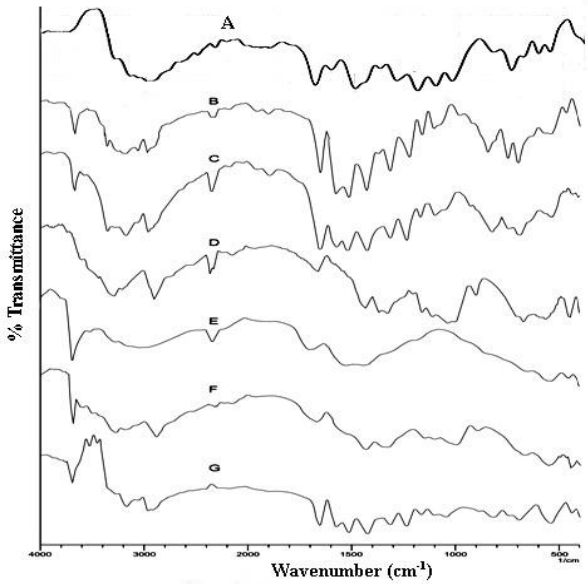

Figure 1: FTIR spectra of : (A) Amlodipine, (B) Atorvastatin (C) Amlodipine and Atorvastatin, (D) Crosscaramellose Sodium, (E) Kyron T_{134}, (F) Crosscaramellose Sodium and Kyron T_{134} and (G) Amlodipine, Atorvastatin, Crosscaramellose Sodium and Kyron T_{134}

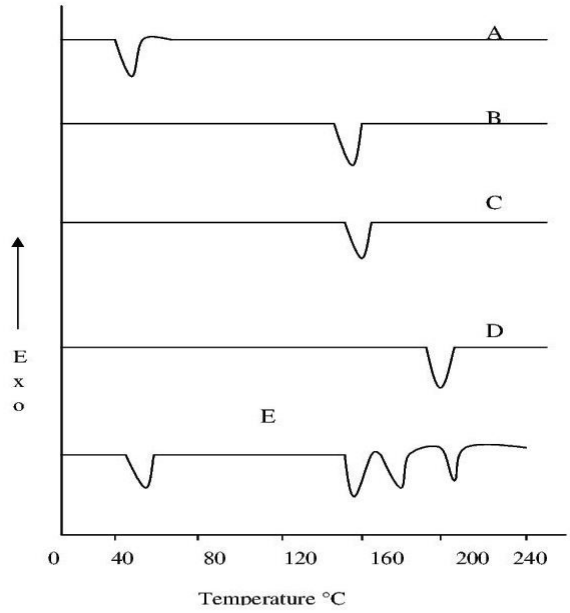

Figure 2: DSC thermograms of : (A) Crosscaramellose Sodium, (B) Amlodipine, (C) Atorvastatin, (D) Kyron T_{134} (E) Amlodipine, Atorvastatin, Crosscaramellose Sodium and Kyron T_{134}

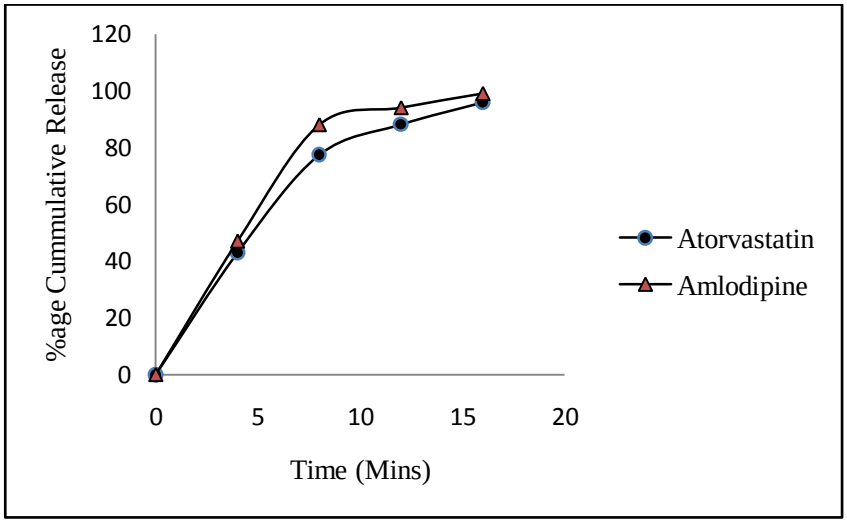

Figure 3: %age Cumulative Release of F8