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FABRICATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF ATORVASTATIN TO IMPROVE DISSOLUTION PROFILE AND SOLUBILITY

HASEEB A[1*], SARFRAZ A[2], IHTISHAM H[3], WAQAS Y[1], RIZWAN H[1]

1: Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan

2: Department of Phamacy, Islamia University Bahawelpur, Bahawalpur, Pakistan

3: Islam medical and dental college Sialkot, Sialkot, Pakistan

*** Corresponding Author: E Mail: haseebahsan110@yahoo.com; Mob: +923338481767**

ABSTRACT

Solubility of poorly water soluble drugs is one of the most emerging issues associated with these drugs to form suitable dosage form that will provide desired pharmacological response. Their low solubility causes elimination of most of the drug from body as such and desired therapeutic levels are not achieved. Different formulations of fast disintegrating tablets (FDT's) were prepared that varied in concentration of β-cyclodextrin and disintegrants as well as in preparation techniques. Results were statistically analyzed by one way ANOVA test and p value was determined to check significant results. Results had shown that formulation F4 prepared solid dispersion of drug, polymer and disintegrant (kyron T_{134}) achieved maximum release of drug 99% within 15 minute. Scanning electron microscopy (SEM) photographs had shown pores on surface tablets that enhanced water penetration and improved dissolution. X-Ray diffraction (XRDP) had shown that FDT's converted from crystalline to amorphous form. So solubility was enhanced. Disintegration time was present between 26 to 67 S. Dispersion time was present between 24 to 47 S. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) results confirmed the stability of formulations and complex formation between drug, β-cyclodextrin and disintegrants. So it could be concluded that stable FDT's of Atorvastatin with β-cyclodextrin and disintegrants can be made with enhanced solubility and dissolution profile of drug.

INTRODUCTION

Majority of available drugs are poorly water soluble. Pharmaceutical industry faces many problems regarding solubility of such drugs [1]. This problem is associated with more than 40% of drugs that are available. Such low solubility of these drugs leads towards poor dissolution in gastrointestinal tract that results in low levels of oral absorption and bioavailability. Solid dispersions and inclusion complexes are used more conventionally to form complex of these drugs with host molecules to enhance solubility [2, 3]. Delivery of such kind of drugs in this form can promote dissolution, absorption and ultimately bioavailability by reducing particle size or converting their nature from crystalline to amorphous [4]. Different researchers described that this improved dissolution may be due to Kelvin's law i.e. solubility is enhanced due to amorphous state or small particle size or it may be due to increase in surface area or improved wetting may occur because of hydrophilic carriers [5].

The improved dissolution rate of drug can be ascribed to (i) an increased solubility of the drug because of its amorphous state or small particle size (Kelvin's law) (ii) an increasing surface area available for drug dissolution because of the small size of the drug particles and (iii) an improved wetting of the drug caused by the hydrophilic carrier [6].

Patient compliance is also an important factor for success of drug therapy but more crucial in chronic conditions. About 50% of patients do not comply with medication especially in pediatric or elderly patients. Poor compliance with medication can lead to morbidity, death, and increase the cost of health care. Unpleasant taste of medication is formulation related problem that has a vital role in medication compliance. These problems can be reduced/solved by using various techniques. One of them is fast dissolving tablets by using various superdisintegrants along with hydrophilic carriers such as β-cyclodextrin [7].

Proper selection of dosage form can enhance patient compliance. For example, transdermal drug delivery system improves patient's compliance by reducing dosage of drug and ease of administration. Similarly, if the patients have difficulty in swallowing because of pathological condition or size of the dosage form, Fast disintegrating tablets (FDT's) will help in such scenario in improving patients' compliance [8].

This is beneficial for pediatric and elderly population that cannot easily swallow intact tablets. According to FDA, FDT is ''a solid

dosage form containing medicinal substances which disintegrates rapidly, usually within a few s, when placed upon the tongue.'' In such dosage form dissolution and absorption occurs simultaneously with disintegration of medication. It can be administered with or without water. FDA drafted guidelines for the development of FDT's for pharmaceutical industry to meet quality standard. Ideally, FDT's weight should be less than 500 mg to maintain ease of administration and it should disintegrate in less than 30 S in United States Pharmacopeia (USP) [6].

FDT's have attracted most of researchers because these also help in improving solubility, dissolution and ultimately bioavailability of poorly water soluble drugs. Certain carriers are used in these tablets that aids in rapid disintegration within oral cavity. These include kyron T_{134}, crospovidone, pregelatinized starch, sodium starch glycolate, crosscarmellose sodium etc. along with hydrophilic moieties e.g. β-cyclodextrin that influence their solubility as well as rapid disintegration [9, 10].

Atorvastatin, belongs to BCS class II having low solubility and high permeability. It is poorly water-soluble 3-hydroxy-3-methyl glutaryl CoA (HMG-CoA) reductase inhibitor. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in cholesterol biosynthesis, a potent lipid-lower ingredient, and used as hypolipidemic agent [10].

In present work efforts have been made to enhance solubility of Atorvastatin by fabricating FDT's from solid dispersion of drug, polymer and disintegrants as well as their physical mixture. These tablets were then evaluated to check enhancement in solubility by using various parameters and finally conclusion was made to select optimized formulation.

MATERIALS AND METHOD

Materials

Atorvastatin was obtained as gift sample from Getz pharmaceuticals Islamabad, Pakistan. B-cyclodextrin and methanol were purchased from Sigma Aldrich Chemie GmbH, Steinheim, Germany. Kyron T_{134}, sodium starch glycolate and saccharine were obtained from Warrick pharmaceuticals Islamabad, Pakistan. Magnesium stearate and lactose were taken from department chemical store. All the chemicals were used of high purity grade.

Preparation of fast disintegrating tablets

Three different types of FDT's formulations were prepared: solid dispersions composed of drug and carrier in which super

disintegrants were incorporated; solid dispersions composed of drug and carrier physically mixed with super disintegrants; and physical mixtures of drug, carrier and super disintegrant along with other ingredients as shown in (Table 1).

FDT's were prepared by slight modification of [9]. Solid dispersions of Atorvastatin were prepared by dissolving drug in methanol. Solution of drug was prepared in methanol and β-cyclodextrin in water. Predetermined amount of drug and β-cyclodextrin were weighed on an electronic weighing balance and dissolve in respective solvents. Both solutions were sonicated until clear solution was formed. Then both these solutions were mixed so that proper reaction took place between drug and carrier to make solid dispersions. After that solution was kept on hot plate stirrer to evaporate solvent and kept solid dispersions in lyophilizer for 24 h to become freeze dried. In formulations where superdisintegrants needed to be added in solid dispersion were weighed and dissolved in solution containing β-cyclodextrin and then mixed with drug solution. In first type of formulations drug, carrier and superdisintegrants were collectively used to prepare solid dispersions while in second type of formulations solid dispersions of drug and carrier were first prepared and then physically mixed with superdisintegrants. Third type of formulations was just physically mixture of drug, carrier and superdisintegrants. Then all these formulations were compressed into FDT's using 8 mm round flat beveled edge punches on a 10 station rotary tableting machine. Total 15 formulations were prepared by varying concentration of carrier and super disintegrants by using these three different approaches five from each [9].

Table 1: Composition of fast disintegrating tablets

Ingredients (mg)	FDT's containing solid dispersions of drug, carrier and superdisintegrants (F1-F5)					FDT's containing solid dispersions of drug and carrier physically mixed with superdisintegrants (F6-F10)					FDT's containing physically mixer of drug, carrier and superdisintegrants (F11-F15)				
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Atorvastatin	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Kyron-T_{134}	8	16	-	16	-	8	16	-	16	-	8	16	-	16	-
Sodium starch glycolate	8	-	16	-	16	8	-	16	-	16	8	-	16	-	16
β-cyclodextrin	60	60	60	80	80	60	60	60	80	80	60	60	60	80	80
Mg-Stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Lactose	85	85	85	65	65	85	85	85	65	65	85	85	85	65	65
Orange Flavor	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Saccharine Sodium	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Total Weight	200mg					200mg					200mg				

Characterization of fast disintegrating tablets

Angle of repose

Angle of repose was calculated by using Funnel method [10];

$$\text{Tan}\theta = \frac{h}{r} \quad [1]$$

Where θ = angle of repose, h= height of cone and r = radius of cone. Angle of repose less than 30°C shows the free flowing properties of the material.

Bulk density

Known mass of powder (M) was weighed on electronic weighing balance (Shimadzu AUW220D) and poured into graduated cylinder. After this bulk volume (Vb) was noted and bulk density was calculated by using following equation;

$$pb = \frac{M}{Vb} \quad [2]$$

Where pb = bulk density, M = mass of the powder and Vb = bulk volume of the powder.

Tapped density

The measuring cylinder containing weighed amount of the powder was tapped for specified number of tapings and time. The volume (Vt) occupied by the powder after tapping and mass (M) was noted. Tapped density was calculated by using equation;

$$pt = \frac{M}{Vt} \quad [3],$$

Where pt = tapped density, M = mass of the powder and Vt =Tapped volume of the powder.

Carr's compressibility index

Carr's compressibility index was calculated by following equation.

$$\text{Carr's index} = Vb - \frac{Vt}{Vb} \times 100 \quad [4]$$

Where Vb = bulk volume of the powder and Vt = tapped volume of the powder. Carr's index between 13 -19% indicates good flow and more than 21% shows poor flow.

Hausner ratio

Hausner ratio was calculated using following equation.

$$\text{Hausner ratio} = \frac{pt}{pb} \quad [5]$$

Where ρt = tapped density and ρb = bulk density. Hausner ratio less than 1.25 shows better flow while more than 1.25 shows poor flow [10].

FTIR spectroscopy

FTIR spectra were obtained between 400 and 4000 cm^{-1} by using IR spectrophotometer (Tensar27) to confirm the formation of copolymer. FTIR spectra of individual ingredients and tablets were taken. Samples were prepared by finely grinding tablets with KBr and by exposing to the infrared radiation [11].

Thermal analysis

DSC and TGA analysis FDT's tablets and all ingredients were taken to determine stability of ingredients in prepared tablets. DSC (Q600 TA USA) was done by heating the

samples from ambient to 400 °C at the heating rate of 10 °C/min in a nitrogen atmosphere at flow rate of 10 mL/min. Thermal stability of copolymer was studied by TGA (Q600 TA USA) at temperature range from 0 °C to 800 °C under inert nitrogen atmosphere [11].

Hardness of FDT's

Tablets hardness was measured to find the strength that can be beard by tablets during storage and transportation. So that tablets might be able to bear transportation effects. Ten tablets were selected randomly and their average weight was calculated. Monsanto hardness tester was used to measure tablet hardness in kg/cm^2. Average of three values was determined.

Thickness and weight variation

Tablets thickness was measured by using Verneir caliper. Tablet was placed in between two arms of caliper. Average of three values was calculated Weight variation was determined by taking twenty tablets and weighing them on electronic weighing balance to determine average weight. At the end, individual weight was compared with average weight [12].

Friability

Friability of tablets was determined by using Roche friabilator (Pharma Test, Germany). Twenty tablets were weighed and placed in the drum of the friabilator at a speed of 25 rpm. The tablets were allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dusted using muslin cloth and re-weighed. Then friability was measured by calculating % weight loss of 20 FDT's. Less than 1% friability should be acceptable [12].

Tablet disintegration

Tablet disintegration apparatus was used. Six tablets were taken and placed individually in tubes and properly covered. The temperature of medium was maintained at 37±2°C and timely noted by thermometer. The time taken by the tablet to disintegrate completely was noted.

Wetting time

Ten millilitres of the buffer solution of pH 6.80 as saliva was taken in petri dish. A circular tissue paper having diameter 8 cm folded twice was placed in the petri dish. Single mouth disintegrating tablet was placed on tissue paper and time for complete wetting was noted [13].

Solubility studies

Solubility studies of pure drug (Atorvastatin), physical mixture of drug and β-cyclodextrin and FDT's prepared by solid dispersions and physical mixture was conducted to compare solubility of our formulations with pure drug. We took predetermined amount of formulations that contain 20 mg of drug and

dissolved them in 10 ml of phosphate buffer of 6.8 and 1.2 pH in a conical flask and shaked using water bath shaker for 48 h at 37±0.5 ºC. Then samples were withdrawn and analyzed at 226 nm.

Dissolution study

Dissolution studies of FDTs were performed on USP type-II apparatus. The speed of apparatus was set at 50 rpm. 900 millilitres of phosphate buffer solution of pH 6.80 was taken as dissolution medium in each vessel of the apparatus. A single mouth dissolving tablet was dipped in each of the dissolution vessels and temperature of medium was kept at 37±0.5°C. The dissolution sample was taken from each vessel at regular intervals and was replaced by equal volume of freshly prepared media. Absorbance was measured by using UV/Vis spectrophotometer (UV 1700, Shimadzu, Japan) at its absorbance of 226 nm [14].

In vitro dispersion time

About 6 ml phosphate buffer of pH 6.80 was taken in a beaker of 10 ml capacity. A tablet was placed in that beaker and time required for complete dispersion of tablet was noted. The experiment was performed thrice for each formulation.

Water absorption ratio It is the amount of water absorbed by the tablet in a unit time. Six milliliters of water was taken in a Petri dish of internal diameter 6.50 cm. A piece of tissue paper folded twice was placed in the Petri dish. A tablet was weighed before placing onto tissue paper in Petri dish and time taken by tablet for complete wetting was noted. Wetted tablet was reweighed and water absorption ratio was calculated by using a previously reported formula.

Drug content uniformity

Twenty tablets were crushed into fine powder. A quantity equivalent to 15 mg was taken and diluted in phosphate buffer of pH 6.80 leading to first dilution. It was faltered and filtrate was diluted again leading to 2nd dilution. Then sample of 2-3 ml was taken and at its absorbance226 nm was noted on UV/Vis spectrophotometer. The same procedure was repeated thrice and also for the standard. Then amount of the drug present in sample was calculated.

X-ray powder diffraction (XRPD)

Samples were analyzed using an X'Pert PROMPD diffractometer (PANalytical, Almelo, the Netherlands) with a copper anode (Cu Ka radiation, k = 0.15405 nm, 40 kV, 40 mA).X-ray diffraction pattern of selected FDT's will be compared with that of pure drug. This will be performed by measuring 2θ in the range of 4°Cto 50°C with reproducibility of ±0°C –001°C on an X-ray diffractometer[15].

Scanning electron microscopy

For SEM measurements, Atorvastatin based FDT's were attached on metal stubs using double-sided adhesive tape, dried in a vacuum chamber, sputter-coated with a gold layer of 10 nm thick and viewed under high resolution SEM (JSM-840, Joel Instruments, Tokyo, Japan) to describe the shape and morphology as well as to check porosity on tablet surfaces that are helpful in rapid release of drug.

Stability studies

The stability studies of FDT's were performed for three best formulations for a period of three months according to ICH (international conference on harmonization) guidelines. All the physical and *in vitro* tests were performed and any significant changes were observed. Studies were performed under following temperature and humidity conditions 37±1°C, 40±1°C, 50±1°C and RH 75±5%. Samples were taken after 30, 60 and 90 days interval and revaluated for above mentioned parameters.

Statistical analysis

All the results were evaluated statistically by using one-way ANOVA after determining mean and standard deviation.

RESULTS AND DISCUSSION

Fifteen formulations of FDT's were prepared by varying concentration of β-cyclodextrin which is used as drug carrier and superdisintegrants. Three different techniques were used to formulate these fifteen formulations. In first group, five formulations were prepared containing solid dispersion of drug, carrier and superdisintegrants. In second group solid dispersion of drug and carrier was prepared and then mixed this solid dispersion with superdisintegrants. In third group, five formulations of FDT's were fabricated just by using physical mixture of drug, carrier and superdisintegrants. We had evaluated these formulations by various parameters and studied effect of carrier, superdisintegrants and method of preparation on release and solubility of Atorvastatinthat was used as model drug. FDT's were first evaluated for micromeritics parameters. Flow properties are very important for powder or particulate material to compress into tablets. Materials that do not have good flow properties are difficult to compress into tablets and ultimately leads towards improper mixing of drug with other ingredients as well as can cause other compression problems. To avoid such issues solid dispersions and physical mixture were evaluated for flow properties such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Results of these rheological parameters are

present in (Table 1). Value of angle of repose was present 21.50 to 26.10. Its value below than 30 is considered good for proper flow of powder material. Results of other rheological parameters are also mentioned in (Table 1) that had shown that these all were lying within pharmacopeia limits. These results had favored that our material was suitable for compression into FDT's and all ingredients were mixed properly before compression. These findings were in agreement of others study [11].

FTIR spectra of drug alone and of various FDT's formulation were taken to ensure complex formation between drug and β-cyclodextrin. Drug spectra had shown that characteristic peeks were present at 3337.90 cm^{-1}, 2968.23 cm^{-1} and 1435.48 cm^{-1} corresponding to cyclic amines, C-H stretching, C=O stretching, O-H bending. These were almost same as reported in monograph for Atorvastatin. FTIR spectra of physical mixture of drug with β-cyclodextrin and superdisintegrants were also taken inorder to compare with FDT's. Characteristic peaks of FTIR spectra of pure drug were present at 3337.90 cm^{-1}, 2968.23 cm^{-1} and 1435.48cm^{-1} as shown in Fig. 2. Similar peaks were present in physical mixture of drug and β-cyclodextrin as well as with superdisintegrants, it confirmed that no interactions were present between drug and β-cyclodextrin and with superdisintegrants. But FTIR spectra of our formulations had shown that characteristic peaks of Atorvastatin were shifted from 3337.90 to 3127.13 cm^{-1} and there was complete absence of characteristic peak present at 1435.48 cm^{-1} that was due toO-H bending. These findings had confirmed that there was complex formation between drug and polymer. Our results were in compliance of study conducted [12].

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	0.629	0.737	23.60	1.17	15.75
F2	0.637	0.729	21.50	1.14	16.50
F3	0.631	0.733	23.80	1.16	14.97
F4	0.619	0.719	25.40	1.16	16.45
F5	0.621	0.727	24.50	1.17	15.50
F6	0.609	0.719	22.60	1.18	16.40
F7	0.629	0.723	24.90	1.14	15.98
F8	0.623	0.751	24.70	1.20	16.57
F9	0.621	0.730	23.80	1.17	15.82
F10	0.597	0.713	26.10	1.19	15.80
F11	0.640	0.727	24.50	1.13	17.26
F12	0.623	0.727	24.80	1.16	15.28
F13	0.623	0.738	24.70	1.18	16.90
F14	0.639	0.746	25.80	1.16	14.50
F15	0.609	0.713	25.60	1.17	16.80

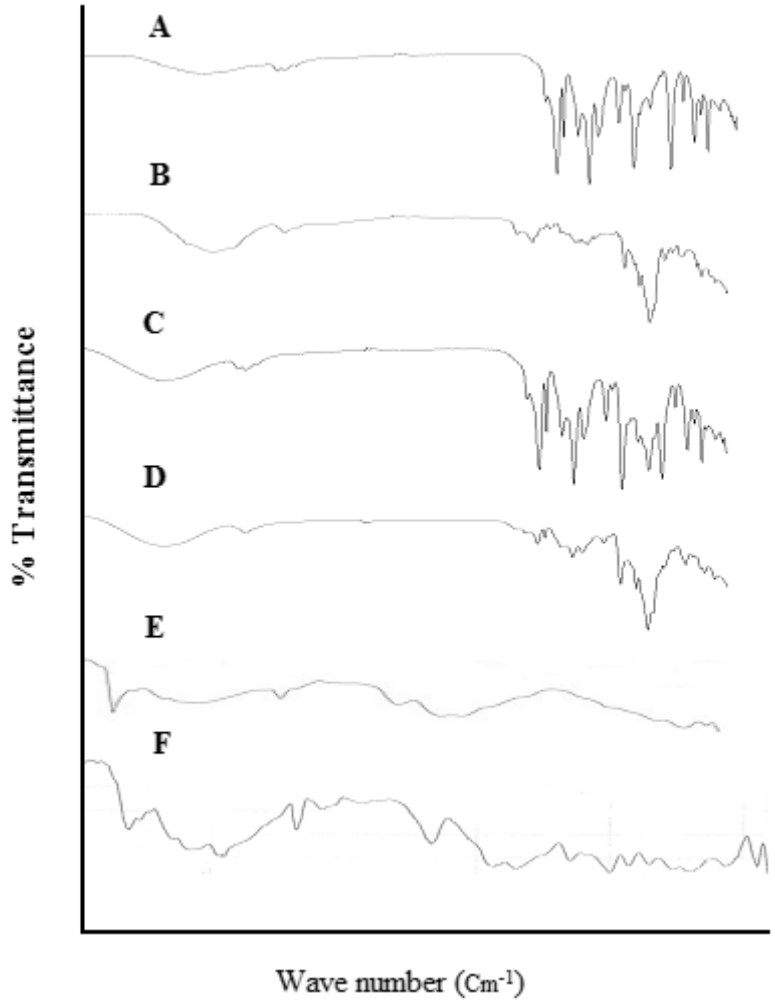

Figure 1: FTIR spectra of (A) atorvastatin (B) β-cyclodextrin (C) FDT's containing physical mixture (D) FDT's containing solid dispersion (E) kyron T134 (F) sodium starch glycolate

Thermal analysis of prepared formulations was performed to check the stability of complexed formed between drug, carrier and superdisintegrants. DSC thermo gram of Atorvastatin alone, physical mixture of drug, carrier and superdisintegrants as well as of prepared FDT's were also taken. It had shown that there was presence of sharp endothermic peak at 126 °C in DSC thermo gram of pure drug and of physical mixture as well. This depicts that there was no interaction was present between drug and polymer. In thermo gram of FDT's characteristic peak of Atorvastatin was disappeared from 126 °C and shifted at higher temperature Fig. 1. This shifting of peaks ensured that there was formation of solid complex between drug, carrier and superdisintegrants. Our results were in compliance with some other studies that disappearance or shifting of peaks confirmed that formation of complex [3].

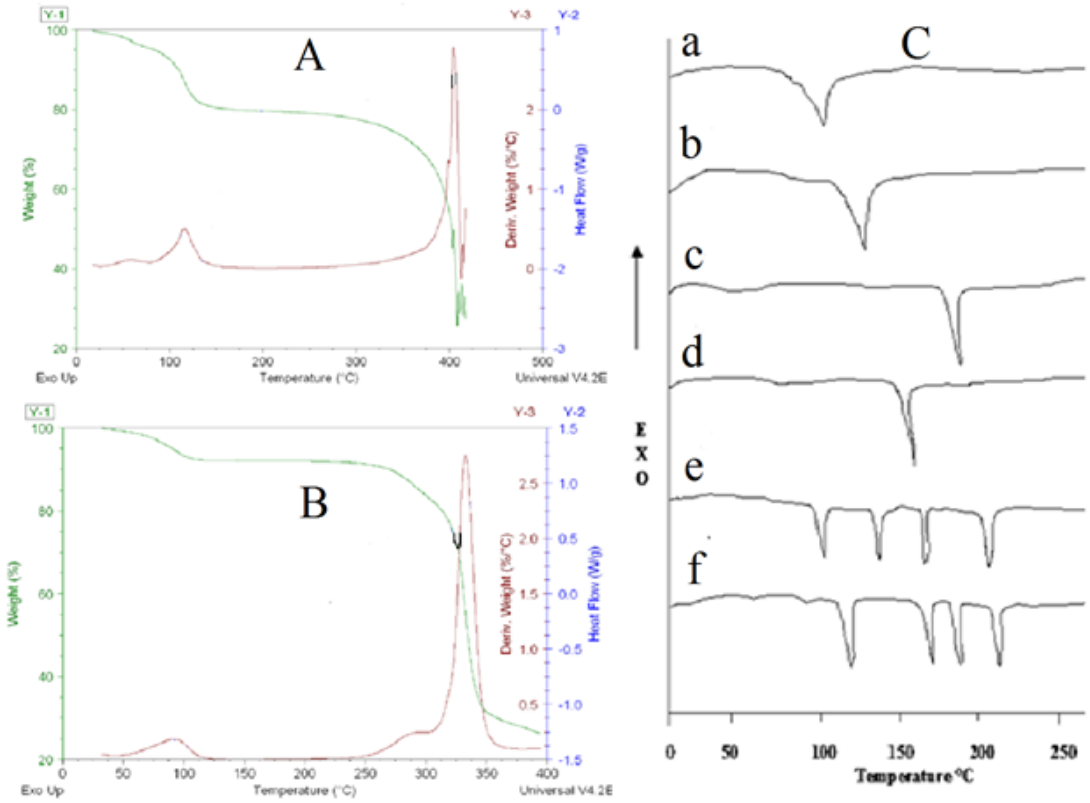

Figure. 2: TGA (A) of physical mixture of drug with β-cyclodextrin and disintegrants (B) TGA of solid dispersion of drug with β-cyclodextrin and disintegrants (C) DSC spectra of (a) β-cyclodextrin (b) atorvastatin (c) kyron T_{134} (d) sodium starch glycolate (e) FDT's containing physical mixture (f) FDT's containing solid dispersion.

After evaluation of pre compression studies, powder was compressed into FDT's. Results of weight variation for all formulations were lie within the pharmacopeial limits as shown in Table 2. This represent that tablets were of proper weight and size. It had also shown that there was consistency present among prepared tablets and minimum batch to batch variation. Hardness generally indicates that tablets are able to bear stress during handling and remain stable during storage. A linear relationship exists between tablet hardness and disintegration time(DT). If tablets are harder than pores present on surface of tablets are so compacted that it's very difficult for water to penetrate within tablets to impart drug release. Increased hardness caused increased in tablet density by reduction in pores. This resulted in the reduction of number of pores in the tablet that hampered the liquid penetration and access to disintegrants particles in the FDT's. As a result reduction in wetting of tablets that ultimately effects the development of proper force, which led to prolongation of DT. The effect of tablet hardness is shown in the SEM photographs Fig. 5. In addition to hardness, lubricant concentration also has great influence on the DT. Magnesium stearate is hydrophobic in nature. When high

concentration of lubricant is used this might cause coating of hydrophilic components of tablet formulations, limiting the wetting of components of formulation especially the disintegrants and drug carrier which are very vital in the disintegration process of the tablet. Subsequently, DT of tablet would increase. Overall results of hardness indicate that they were present within prescribed limits of FDT's. Formulations prepared by solid dispersion had better hardness results as compared to physical mixture. Thickness results had also shown that these were present within acceptable limits. All the tablets had proper thickness[12].

Generally tablets have friability less than 1% is considered good. Friability of all the formulations was less than 0.8% which suggested that tablets had good mechanical strength. Tablets did not show any unnecessary breakdown of the particles when rotated in drum of friabilator. This favored that tablets can bear stress during transportation and storage. Few tablets had slightly high value of friability but not greater than desired limits that might be due to improper mixing of ingredients or compression but overall results were good. Statistically results of friability were tested by using one way ANOVA. Results of ANOVA between the groups had shown that p-value was 0.025 which was less than 0.05. This proved that results were significant. The results within groups were highly significant. It's mean that fariability of tablets were significantly affected by concentration of superdisintegrant, polymer (β-cyclodextrin) and method of preparation.

Table 3: Results of weight variation, hardness, thickness, Friability, disintegration time and wetting time

Code	Weight variation (mg)	HardnessKg/ cm^2	Thickness (mm)	Friability* (%)	Disintegration*time (S)	Wetting* time (S)
F1	199.90	3.30	3.40	0.754±0.00	44±1.15	56±1.25
F2	198.60	3.20	3.35	0.635±0.02	35±1.15	44±1.50
F3	197.87	3.40	3.20	0.560±0.01	40±3.46	49±1.61
F4	198.90	3.30	3.50	0.572±0.02	26±1.15	34±1.58
F5	199.50	3.10	3.40	0.438±0.01	30±1.08	38±0.73
F6	198.54	3.40	2.99	0.650±0.02	55±2.15	64±2.18
F7	199.75	3.20	3.25	0.580±0.01	46±1.25	55±1.25
F8	198.80	3.50	3.20	0.540±0.01	51±1.70	60±1.50
F9	197.72	3.30	3.25	0.590±0.02	38±2.21	42±1.20
F10	199.60	3.60	3.00	0.640±0.03	43±1.15	47±1.70
F11	196.26	3.20	3.10	0.570±0.01	67±1.25	76±1.25
F12	197.85	3.60	3.58	0.420±0.00	55±1.10	69±1.60
F13	195.35	3.40	3.30	0.550±0.02	61±1.15	72±1.80
F14	199.40	3.50	3.28	0.570±0.02	49±1.15	54±1.50
F15	196.60	3.40	3.08	0.450±0.02	53±1.83	58±2.30

***Average of three determinations; SD - Standard deviation**

XRD is one of the most important parameter to be studied when working on solubility enhancement of some poorly water soluble chemical entity. Changes in polymorphic characteristics of certain compounds have great impact on solubility, dissolution as well

as bioavailability. Powder X-Ray diffractogram were taken to found nature of Atorvastatin whether it was crystalline or amorphous. The X-Ray Diffraction pattern of pure drug (Atorvastatin) showed sharp diffraction peaks at 2θ values of 18.64, 24.98, and 33.34 while FDT's showed no such characteristics peaks at 2θ Fig. 3. The absence of characteristics peak in formulation indicated that drug had converted from crystalline to amorphous form. As a result solubility of Atorvastatin was enhanced in FDT's prepared by using β-cyclodextrin and superdisintegrants because amorphous forms are more soluble as compared to crystalline form. Similar results were obtained in another study [13].

Morphology and size of FDT's was determined by using scanning electron microscopy. SEM images had shown that pores had been created on surface of tablets Fig. 4. These pores had favored entrance of water inside of tablets to fasten the release of drug from tablets and ultimately solubility was enhanced. There was slight difference in appearance of some tablets that had slightly lesspores but overall tablets were spherical with uniform pores size.

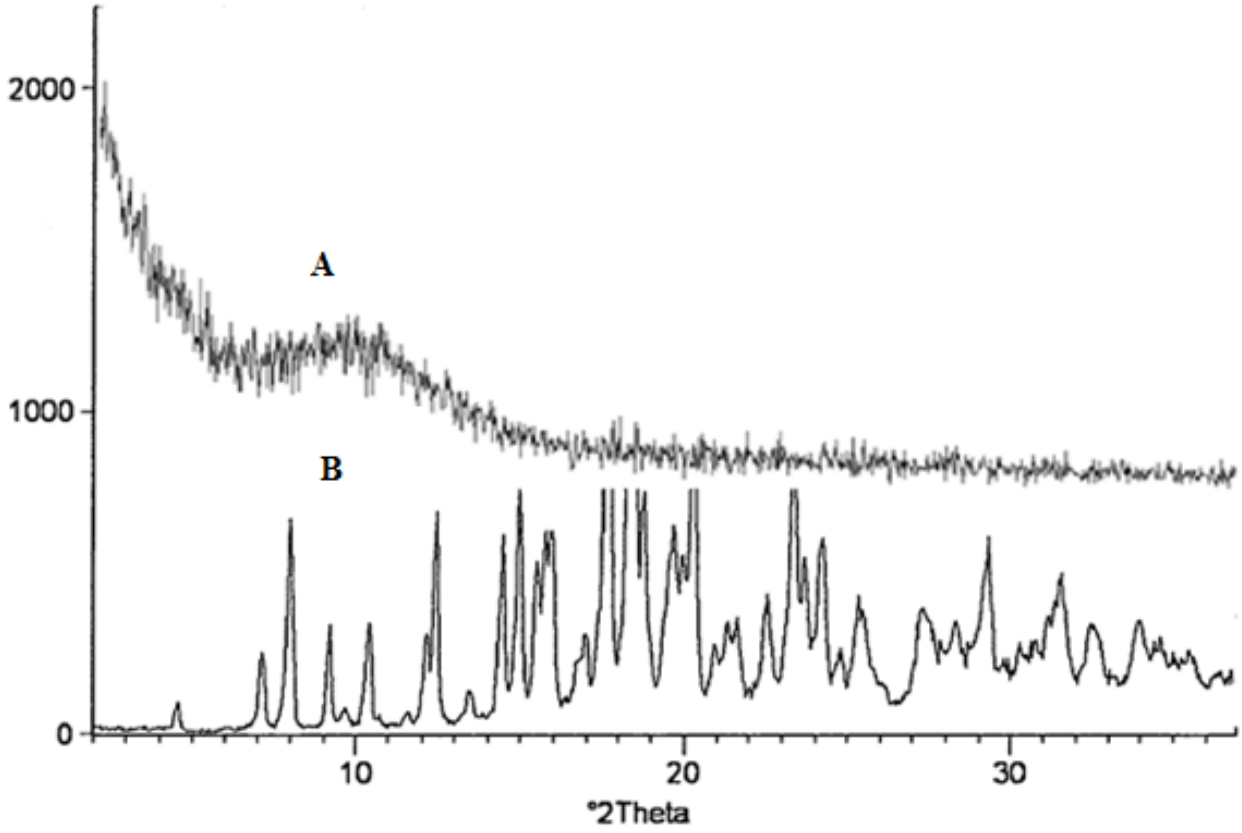

Figure 3: X-Ray diffractogram of (A) formulation (B) atorvastatin

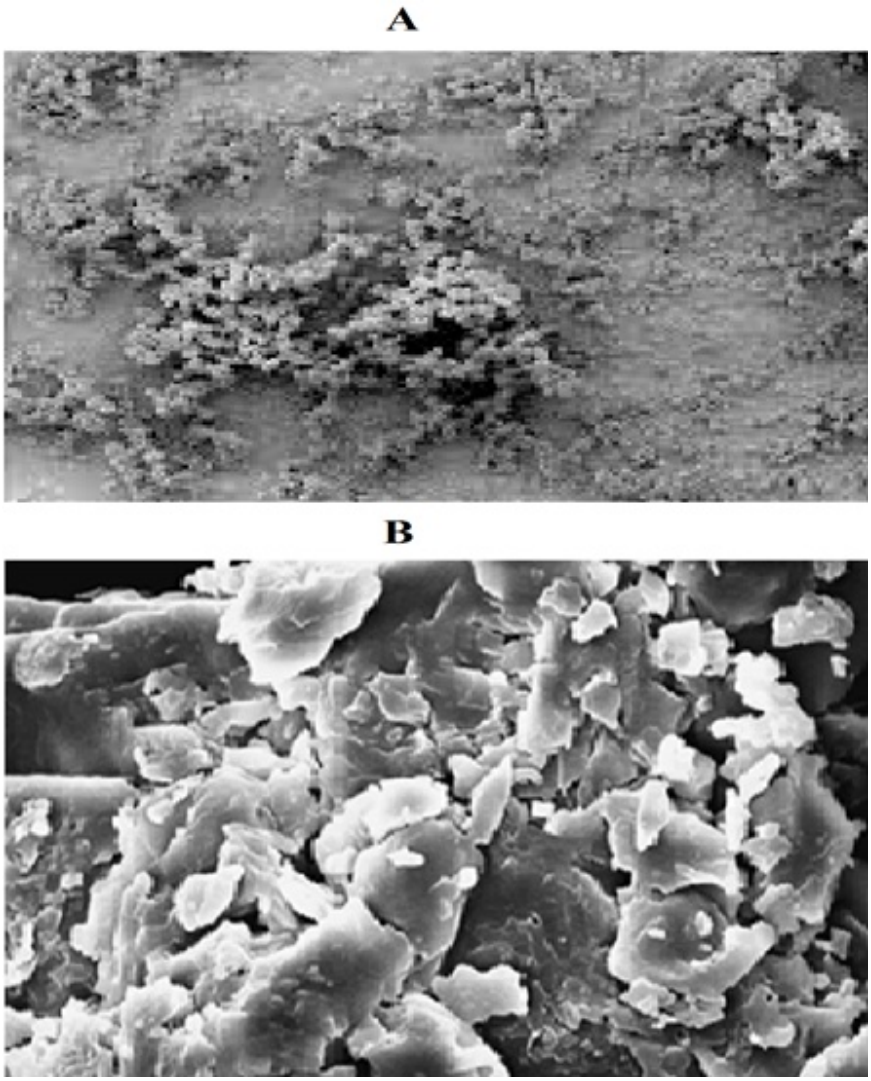

Figure 4: SEM images of formulation F4 at different time interval.

Wetting time is the indication of hydrophobicity of the ingredients. The lower the wetting time faster will be disintegration. Wetting time for all 15 formulations was less than 90 S lying between 34 to 76 S as shown in (Table 3). It was lowest for F4 formulation containing drug and β-cyclodextrin in ratio of 1:4 and kyron T_{134} as superdisintegrant that was prepared by making solid dispersion of drug, polymer and superdisintegrants. Overall evaluation of results of wetting time had revealed that, it was lowest for formulation prepared by solid dispersion technique. It was also observed that F9 contain same composition but had more wetting time than F4. Difference between these two formulations was method of preparation. Similarly F5 was prepared by same method but had sodium starch glycolate as disintegrant rather than kyron T_{134}. It also

had greater wetting time than F4. So we can say that in addition to method of preparation, nature and concentration of polymer and disintegrant had also great influence on wetting time of FDT's and ultimately on solubility of drug. The results of one way ANOVA had shown that p-value for wetting time between the groups was 0.036 that was less than 0.05. It indicates that results were significant and wetting of tablets was affected by method of preparation, nature and concentration of polymer and disintegrant. Wetting time within groups was highly significant which indicates that wetting of tablets was greatly affected by the concentration of polymer and disintegrants.

Disintegration time for FDTs is generally below 1 min and time that patient can experience is 5 to 30 S (Table 3).Rapid uptake of water from medium can cause swelling of tablets and ultimately quick disintegration to produce bursting effect. This results in fast release of drug from its medium into surrounding environment and hence solubility of loaded drug enhanced. Similar to wetting time it was also lowest for F4. By these results it become cleared that β-cyclodextrin and kyron T_{134} complexed with drug through solid dispersion had low DT than formulations just prepared by physical mixture. Results of both wetting time and disintegration time studies were in agreement with specifications indicating that all formulations would definitely disintegrate in oral cavity within specified time period.Results of DT were significant that also proved that method of preparation, concentration and nature of disintegrant and polymer had positive influence on DT. Wetting volume was present between 10 to 27 ml. It was also lowest for F4.

In vitro dispersion test was performed for all of the formulations. This test was used to find dispersion time for tablets by using petri dish method. Dispersion of tablets was affected by swelling which was due to disintegrants. Formulation F4 containing drug and β-cyclodextrin in ratio of 1:4 and kyron T_{134} as disintegrant had lowest dispersion time among all formulations. These results had shown that kyron T_{134} was better choice as disintegrant than sodium starch glycolate. All three groups of formulations had same composition but vary in method of preparation. In single group composition was varied to determine the influence of concentration of polymer on solubility enhancement and for the selection of better disintegrant that can impart rapid release than other. The order in which better dispersion test results were obtained is FDT's containing solid dispersion of drug, carrier

and disintegrant > FDT's containing solid dispersion of drug and carrier physically mixed with disintegrant > FDT's containing physically mixer of drug, carrier and disintegrant as shown in (Table 4). P value was 0.018 for dispersion time.

Water absorption ratio was used to determine that how much water was absorbed by the tablets which ultimately effect the disintegration of the tablets. As more water is absorbed then more rapid will be disintegration. As value of water absorption ratio increases it indicates that rapid breaking of tablets and therefore faster disintegration. This disintegration ultimately effect dissolution rate of tablets that is directly related with solubility of drug. As water absorption ratio increases then dissolution, bioavailability and solubility are also increased. All the formulations had greater water absorption ratio than original weight. This parameter favored formulation F4 that had absorbed water approximately double than its original weight containing solid dispersion of drug, carrier and Kyron T_{134} as disintegrant (Table 4). Overall results of water absorption ratio were present well within specified limits. Results of one way ANOVA had shown that p-value for water absorption ratio was significant which indicates that concentration of polymer and disintegrants effect the tablet disintegration. Solubility studies of pure drug, physical mixture and FDT's were performed to compare them with each other. It was observed that solubility of pure drug within buffer media of 6.8 and 1.2 pH was very low that was upto 20% and 7% respectively within 48 h. Solubility of physical mixture of drug and polymer had improved as compared to solubility of alone drug but it was not upto to the mark as it should be to achieve desired results. Results of solubility studies of FDT's had shown that there was great difference in solubility of drug as compared with pure drug and physical mixture. FDT's had solubility in the range of 87-93% for different formulations based upon concentration of β-cyclodextrin, disintegrant nature and concentration and method of preparation. Formulation F4 and F8 had higher solubility values 93% and 90% respectively than others. But overall F4 had maximum solubility among all FDT's. These results shown that solubility of Atorvastatin were enhanced by manufacturing FDT's prepared by solid dispersions. From these results we found that β-cyclodextrin had enhanced solubility when it was used upto 4:1 with drug. When higher concentrations of β-cyclodextrin were used these had no such influence on solubility of drug and it remains

same as in 4:1. So based on solubility studies we judged that β-cyclodextrin enhanced solubility when it was used upto 4:1 with drug and FDT,s prepared by solid dispersions had better solubility enhancement ability as compared to FDT's prepared just by physical mixture because F4 was prepared by solid dispersion technique.

Dissolution studies were carried out in 6.8 and 1.2 pH phosphate buffer to determine *in vitro* drug release studies. Dissolution studies were performed for FDT's prepared by different methods and for commercially available tablets. Results had shown that there was a marked difference in release of commercially available tablets of Atorvastatin and FDT's prepared using β-cyclodextrin and different disintegrants. Maximum release of drug was observed for FDT's within 15 min but there was no significant release was observed in case of commercially available tablets. There was maximum release of drug in formulation F4 that was 99% in 15 min Fig. 1. These findings also supported our solubility studies that were also maximum for F4. Overall values of drug release were present between 93-99% that was far better than commercially available tablets. These results may also be due to the increase in pores on surface area of tablets as shown in SEM image Fig. 4 that ultimately had absorbed more water from dissolution media and shown better release than commercially available tablets.

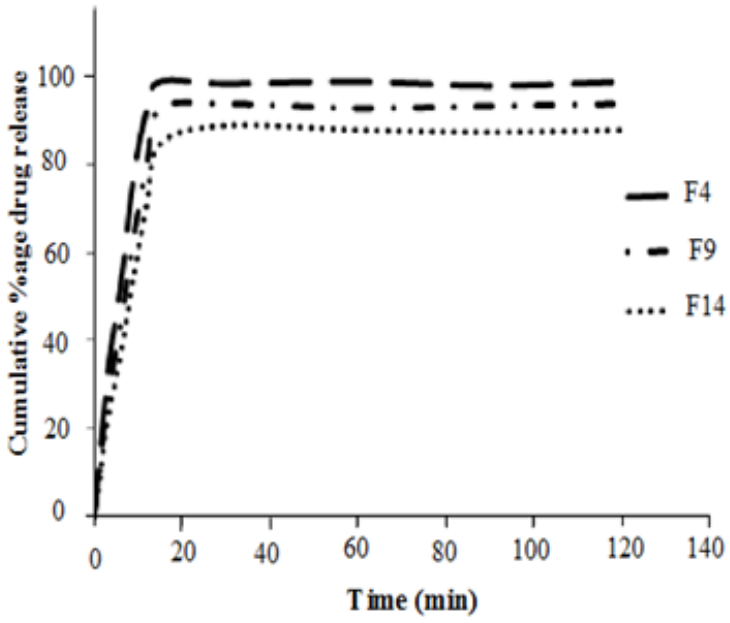

Figure 1: Drug release curve of F4, F9 and F14 at pH 6.8.

Based on the findings of dissolution studies of various formulation we found that β-cyclodextrin had influenced solubility of Atorvastatin used as model drug in this study. As a result *in vitro* dissolution was enhanced. When dissolution results of various formulations were compared based on method of preparation then it was found that FDT's containing solid dispersions had better release rate than FDT's containing physical mixture of same concentration of all constituents.

Statistically significance of results was determined by ANOVA. Results were considered significant when probability level was less than 0.05. Most of the results were significant for different variables.

Stability studies of three best formulations were conducted for six month period. The tablets were kept under accelerated conditions of temperature and humidity 35±5°C and 75%±5% respectively. The sample were taken after 1, 2,3,4,5 and at the end of 6 month. The tablets were evaluated for different parameters. The results had indicated that there were no significant variations occurred in drug content and *in vitro* dispersion time at the end of 6 months. It means that our formulations were stable under different accelerated conditions of temperature and humidity.

Table 4: Results of wetting volume, dispersion time, pH. of tablet solution and water absorption ratio

Code	Wetting* volume (ml)	Dispersion* time (S)	pH of tablet Solution	Water* absorption ratio
F1	22±2.50	40±1.73	7.40	1.80±0.02
F2	15±1.10	31±1.15	7.30	1.80±0.05
F3	18±1.20	32±1.15	7.10	1.40±0.01
F4	10±1.18	24±0.58	6.90	2.30±0.03
F5	12±2.18	27±1.58	7.10	2.10±0.05
F6	24±0.58	43±0.58	7.00	1.70±0.04
F7	18±1.15	34±1.15	7.20	1.80±0.06
F8	21±1.00	38±1.73	7.10	1.70±0.08
F9	13±1.25	26±1.15	6.80	2.00±0.33
F10	15±1.25	30±1.25	6.90	1.80±0.25
F11	27±1.78	47±1.73	7.10	1.60±0.23
F12	19±1.10	39±1.15	7.20	1.70±0.20
F13	25±1.50	43±2.18	7.10	1.60±0.04
F14	17±1.80	31±0.58	7.00	1.80±0.05
F15	20±1.10	36±1.73	7.10	1.90±0.01

***Average of three determinations; SD - Standard deviation**

CONCLUSION

From this study it was concluded that solubility of Atorvastatin can be enhanced by using β-cyclodextrin as polymeric carrier along with certain disintegrants to impart rapid disintegration of FDT's. From prepared various formulations of FDT's we had found that formulation containing β-cyclodextrin in 4:1 with drug prepared by using solid dispersion was best among all. That had kyron T_{134} as disintegrant.

REFERENCES

[1] Keralia RA, Soni TG, Thakkar VT, Gandhi TR and Patel RC, Formulation and

physical characterization of microcrystals for dissolution rate enhancement of tolbutamide, Int. J. Res. Pharma. Sci. 1, (2010), 69 - 77.

[2] Craig DQM, The mechanisms of drug release from solid dispersions in water-soluble polymers, Int. J. Pharma. 231, (2002), 131 - 144.

[3] Ford JL, The current status of solid dispersions, Pharm. Acta. Helv. 61, (1986), 69 - 88.

[4] Leuner C andDressman J,Improving drug solubility for oral delivery using solid dispersions,Eur. J. Pharm. Biopharm. 50, (200),47 - 60.

[5] Chow AHL, Hsia CK, Gordon JD, Young JWM and Vargha-Butler EI,Assessment of wettability and its relationship to the intrinsic dissolution rate of doped phenytoin crystals, Int. J. Pharm. 126, (1995), 21 - 28.

[6] Rahman Z, Siddiqui A and Khan MA,Orally disintegrating tablet of novel salt of antiepileptic drug: Formulation strategy and evaluation,Eur. J. Pharma. Biopharma. 85, (2013), 1300 – 1309.

[7] Madgalkar AR, Bhalekar MR and Padalkar RR, Formulation design and optimization of novel taste masked mouth dissolving tablets of tramadol having adequate mechanical strength, AAPS. Pharm.Sci.Tech. 10, (2009),574 - 581.

[8] Padala KP, Hinners CK and Padala PR, Mirtazapine therapy for dysgeusia in an elderly patient prim care companion, J. Clin. Psychiatry. 8, (2006),178 - 180.

[9] Srinarong P, Faber JH, Visser MR, Hinrichs WLJ and Frijlink HW. Strongly enhanced dissolution rate of fenofibrate solid dispersion tablets by incorporation of super disintegrants.Eur J. Pharma. Biopharma.73, (2009),154 - 161.

[10] Sarfraz RM, Khan HU, Mahmood A, Ahmad M, Maheen S and Sher M, Formulation and evaluation of mouth disintegrating tablets of atenolol and atorvastatin, Indian. J. Pharm. Sci. 77, (2015), 83 - 90.

[11] Sarfraz RM, Ahmad M, Mahmood A, Khan HU, Sher M, Maheen S, Bashir I, Iqbal A and Ahsan H,Formulation and in-vitro evaluation of novel atorvastatin - amlodipine orodispersible tabletsInt. J. Bio. Pharm. Alli. Sci. 3 (2014), 941 - 951.

[12] Inayat BP, Prakash RS and Pritish K, Formulation design and optimization of novel mouth dissolving tablets for venlafaxine hydrochloride using sublimation technique, J. Pharm. Res, 6, (2013), 593-598.

[13] Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A and Iida K, Preparation and evaluation of a compressed tablet rapidly

disintegrating in the oral cavity,Chem. Pharm. Bull.44 (1996),2121 - 2127.

[14] Battu SK, Repka MA, Majumdar S, Madhusudan RY, Formulation and evaluation of rapidly disintegrating tablet fenoverine tablets: effect of superdisintegrants, Drug. Dev. Ind. Pharm. 33: (2007), 1225 - 1232.