Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2010; 2(2) 47-55

ISSN: 0975 4415

Research Article

Design And Development Of Fast Disintegrating Tablet Of Felodipine By Vacuum Drying Technique

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ABSTRACT
Felodipine which is used in the present study is a dihydropyridine derivative, that is chemically described as ethyl methyl-4-(2, 3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, widely accepted for its excellent antihypertensive and anti-anginal properties since it is calcium antagonist compound (calcium channel blocker). Felodipine is practically insoluble in water and its dissolution rate is limited by its physicochemical properties. In the present study fast disintegrating tablets of felodipine were prepared by adopting vacuum drying technique to study the effect of different subliming agents with various concentrations on disintegrating time. The powder blend was examined for the pre-compressional parameters. The prepared formulations were evaluated for post-compressional analysis for the parameters like hardness, friability, thickness, wetting time, water absorption ratio, weight variation, *in-vitro* disintegration time, i*n- vitro* dispersion time, i*n-vitro* dissolution study. Drug compatibility with excipients was checked by FTIR studies. The results obtained showed that quantity of ammonium bicarbonate, urea and menthol significantly affect the response variables (P> 0.05). No chemical interaction between drug and excipients was confirmed by FTIR studies. Stability studies carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets decreased significantly (P> 0.05). The results concluded that fast disintegrating tablets of felodipine showing enhanced dissolution rate with increasing the concentrations of subliming agents. Among all the formulations A3 and M3 shows the improved dissolution rate which lead to improved bioavailability and effective therapy by using vacuum drying technique.

Keywords: Felodipine, fast disintegrating tablets, ammonium bicarbonate, urea, menthol.

INTRODUCTION:

In the present study felodipine is used as a model drug, is a dihydropyridine calcium channel blockers, used in the management of hypertension and angina pectoris. It is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes exclusive first pass metabolism, with a bioavailability of only 15 %. It is exclusively metabolized in the gut and the liver and is excreted almost entirely as metabolites, about 70 % of a dose being excreted in urine and the remainder in faeces. The terminal elimination half life is 11-16 hrs after oral administration[1-4] Felodipine is practically insoluble in water. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by decreasing the disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution[5].

The oral route of administration still continues to be the most preferred route due to ease of ingestion, pain avoidance, vessality and most importantly patient compliance[6]. Amongst all the orally administered dosage forms, tablets are most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of changes in various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The pediatric and geriatric patients are of particular concern in order to overcome this, Dispersible tablets[7] and fast-disintegrating tablets[8] have been developed. The target population for these new fast disintegration dosage forms have generally been pediatric, geriatric and bedridden or developmentally disabled patients. Patients with persistent nausea, who are traveling or who have little or no access to water are also good candidates for FDT[9]. With fast dissolving/disintegrating dosage forms increasingly available, it will be likely that prescribers will recommend such products for their non compliant patients. The ease of administration of a fast disintegrating tablet along with its pleasant taste may encourage a patient to adhere to a daily medication regimen.

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Table 1: Composition of fast disintegrating tablets

Ingredients (mg)	A1	A2	A3	M1	M2	M3	U1	U2	U3
Felodipine	5	5	5	5	5	5	5	5	5
Spray dried Lactose	88	80.5	65.5	88	80.5	65.5	88	80.5	65.5
Directly compressed MCC	30	30	30	30	30	30	-	-	-
Mannitol	-	-	-	-	-	-	30	30	30
Crospovidone	6	6	6	6	6	6	6	6	6
Ammonium bicarbonate	7.5	15	30	-	-	-	-	-	-
Menthol	-	-	-	7.5	15	30	-	-	-
Urea	-	-	-	-	-	-	7.5	15	30
Aspartame	6	6	6	6	6	6	6	6	6
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3	3	3
Aerosil	3	3	3	3	3	3	3	3	3

The advantage of FDT formulation is that it combines the advantages of both liquid and conventional tablet formulations, while also offering advantages over both traditional dosage forms[10]. The FDT is increased bioavailability compared to traditional tablets[9]. The main objective of the present investigation to prepare fast disintegrating tablets of felodipine. Crospovidone (CP) was used as superdisintegrant. Effect of various concentrations different subliming agents on disintegration time, wetting time, and dissolution was studied. Different formulations were prepared by vacuum drying technique composition of which is given in (**Table 1).**

Table 2: Tablet weight before vacuum drying (BVD) and after vacuum drying (AVD)

Formulation	Tablet Weight	
	BVD	**AVD**
A1	150 (0.50)	152 (1.22)
A2	150 (0.28)	136 (1.25)
A3	150 (0.32)	120 (1.32)
M1	150 (1.30)	151 (1.40)
M2	150 (0.90)	135 (2.20)
M3	150 (0.55)	122 (1.50)
U1	150 (0.59)	153 (1.25)
U2	150 (0.44)	136 (0.90)
U3	150 (0.42)	121 (0.85)

MATERIALS AND METHODS

Felodipine gift sample was obtained from Cipla Ltd. Bangalore. Crospoviodone gift sample from Maple biotech Pvt. Ltd. Pune. Menthol and ammonium bicarbonate were purchased from Laser chemicals Ahmedabad. Microcrystalline cellulose, Mannitol, Talc, Magnesium stearate, Sodium lauryl sulphate and Urea were purchased from SD Fine chemicals Pvt. Ltd. Mumbai. All other ingredients used were of pharmaceutical grade.

Preparation of Tablets:

Tablets containing 5mg of Felodipine were prepared by direct compression method and the formula used in the study is shown in **Table 1**. The drug, diluents, super disintegrant, sweetener and subliming material were passed through sieve # 40. All the above ingredients were properly mixed together in a poly bag. Talc, Aerosil and magnesium stearate were passed through sieve # 80, mixed and blended with an initial mixer in a poly bag. The powder blend was compressed into tablets using 7 mm bi concave punches on a 'Rimek mini press 1' a 10 station rotary compression machine. After compression the tablets were collected and vacuum dried in a vacuum oven (Lab Care, Bangalore) at 80^0 C until a constant weight was obtained to ensure the complete removal of sublimable component to make the tablet porous **(Table 2).**

Table 3: Solubility study data of Felodipine

S. No	Name of the Solvent/buffer	Concentration (mg/ml) (± SD), n=3
1	Water	0.0012 (0.02)
2	Hydrochloric acid buffer pH 1.2	0.016 (0.092)
3	Hydrochloric acid buffer pH 1.2 + 0.1%SLS	0.021 (0.107)
4	Hydrochloric acid buffer pH 1.2 + 0.3%SLS	0.027 (0.074)
5	Hydrochloric acid buffer pH 1.2 + 0.5%SLS	0.163 (0.014)
6	Phosphate buffer pH 6.5	0.004 (0.040)
7	Phosphate buffer pH 6.5 + 0.1%SLS	0.540 (0.012)
8	Phosphate buffer pH 6.5 + 0.3%SLS	0.222 (0.010)
9	Phosphate buffer pH 6.5 + 0.5%SLS	0.340 (0.029)

Evaluation of disintegration tablets:

The powder blend was subjected for pre-compressional parameters. The prepared tablets were evaluated for hardness, friability, weight variation, thickness, wetting time, water absorption ratio, *in-vitro* dispersion time [11,12], *in-vitro* release study and stability study[13]. The Pfizer hardness tester and the Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu, AX200, Japan). Tablets were weighed individually and compared with average weight. Disintegration time was determined using USP tablet disintegration test apparatus(ED 21, Electrolab, Mumbai) using 900ml distilled water at room temperature. Thickness of tablets was determined by using dial caliper (Mitutoya, model CD-6 CS, Japan). In wetting time study a piece of tissue paper folded twice was kept in a culture dish containing 6ml of distilled water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue

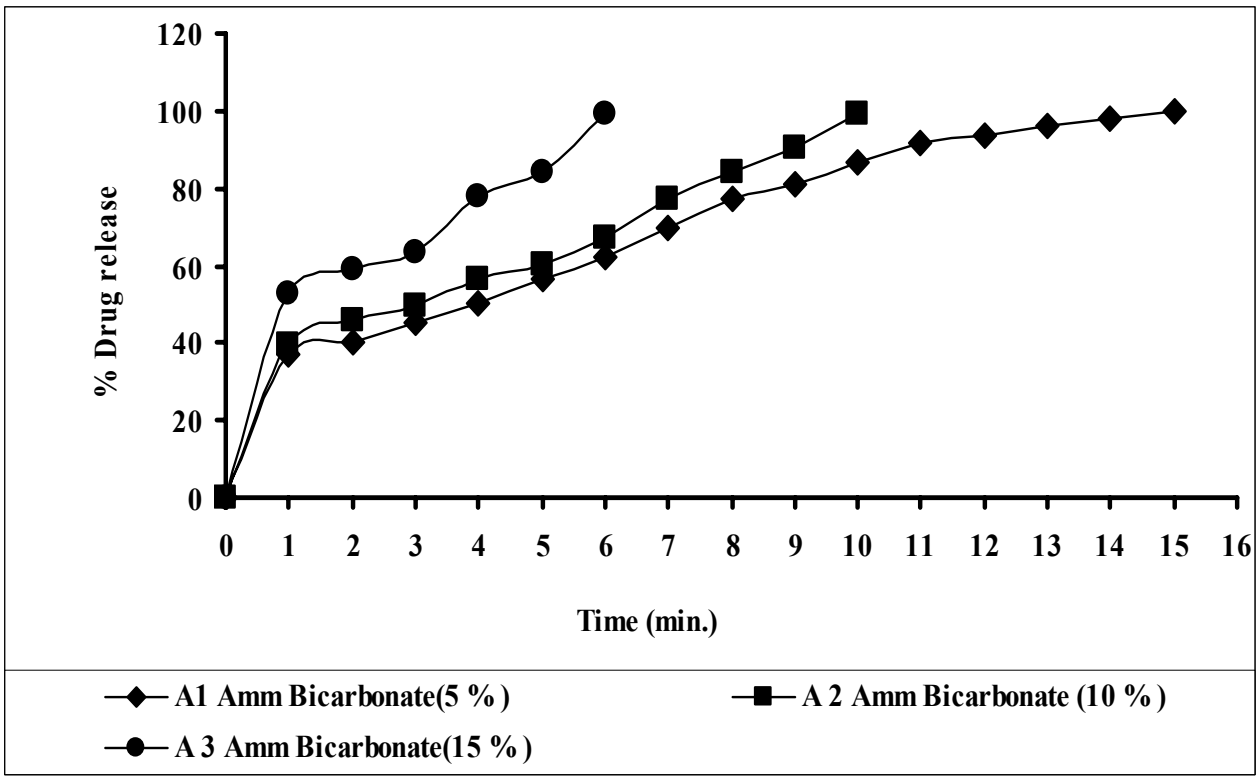

Fig 1: Dissolution profiles of formulations prepared by using Ammonium bicarbonate as subliming agent

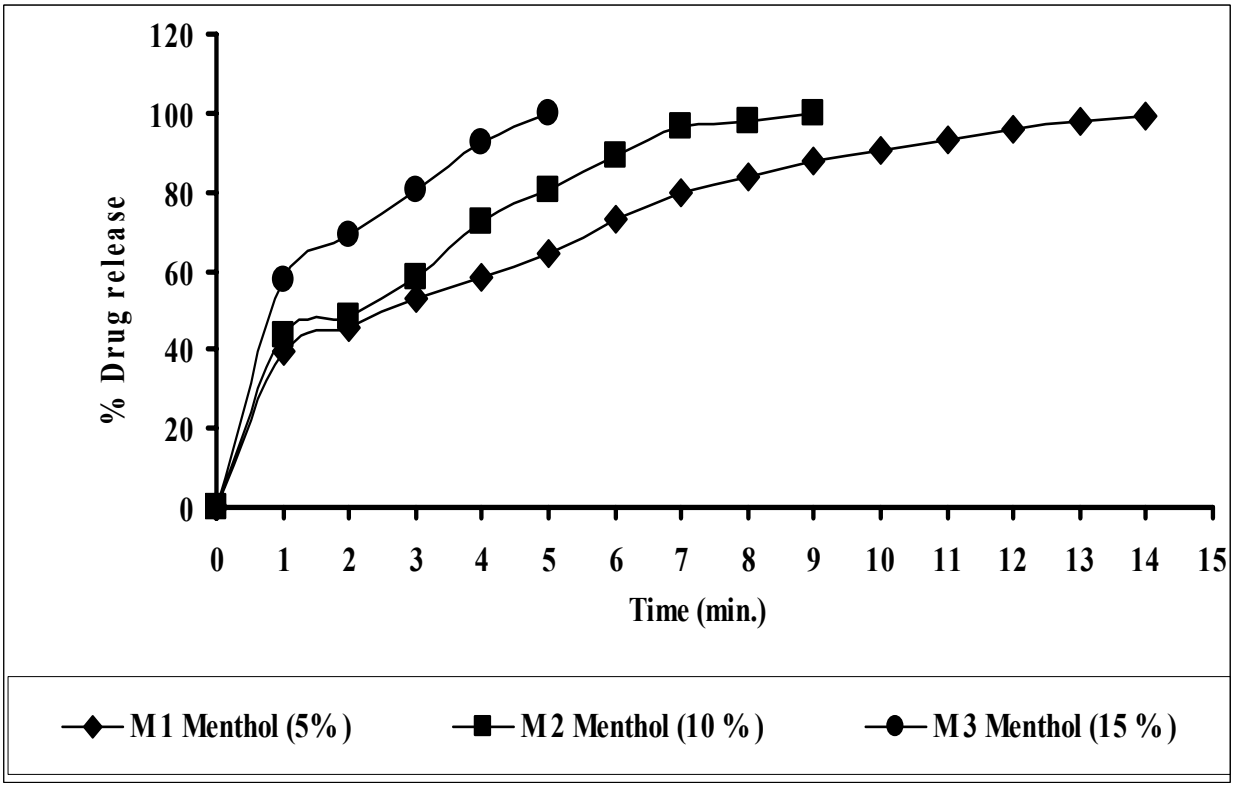

Fig 2: Dissolution profiles of formulations prepared by using Menthol as subliming agent

paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. In water absorption ratio study the same procedure without amaranth was followed. The wetted tablet was weighed and the water absorption ratio, R, was calculated according to the following equation.

$R = 100 (Wa – Wb) / Wb.$

Where,

Wb and Wa were the weights of the tablets before and after study.

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50ml of phosphate buffer pH 6.5 containing 0.1% SLS. Three tablets from each formulation were randomly selected and *in-vitro* dispersion time was performed for drug content analysis a total 10 tablets were weighed and powdered. The powder equivalent to 5mg of Felodipine was taken and

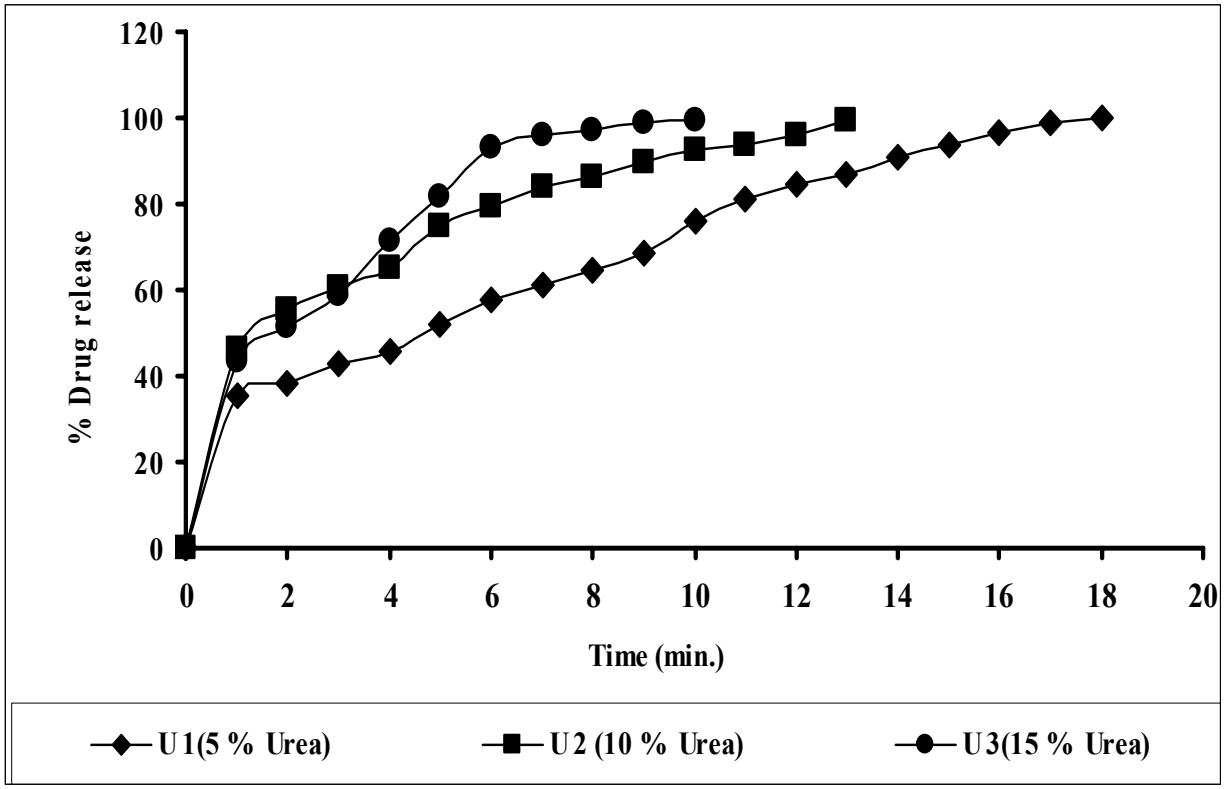

Fig 3: Dissolution profiles of formulations prepared by using Urea as subliming agent

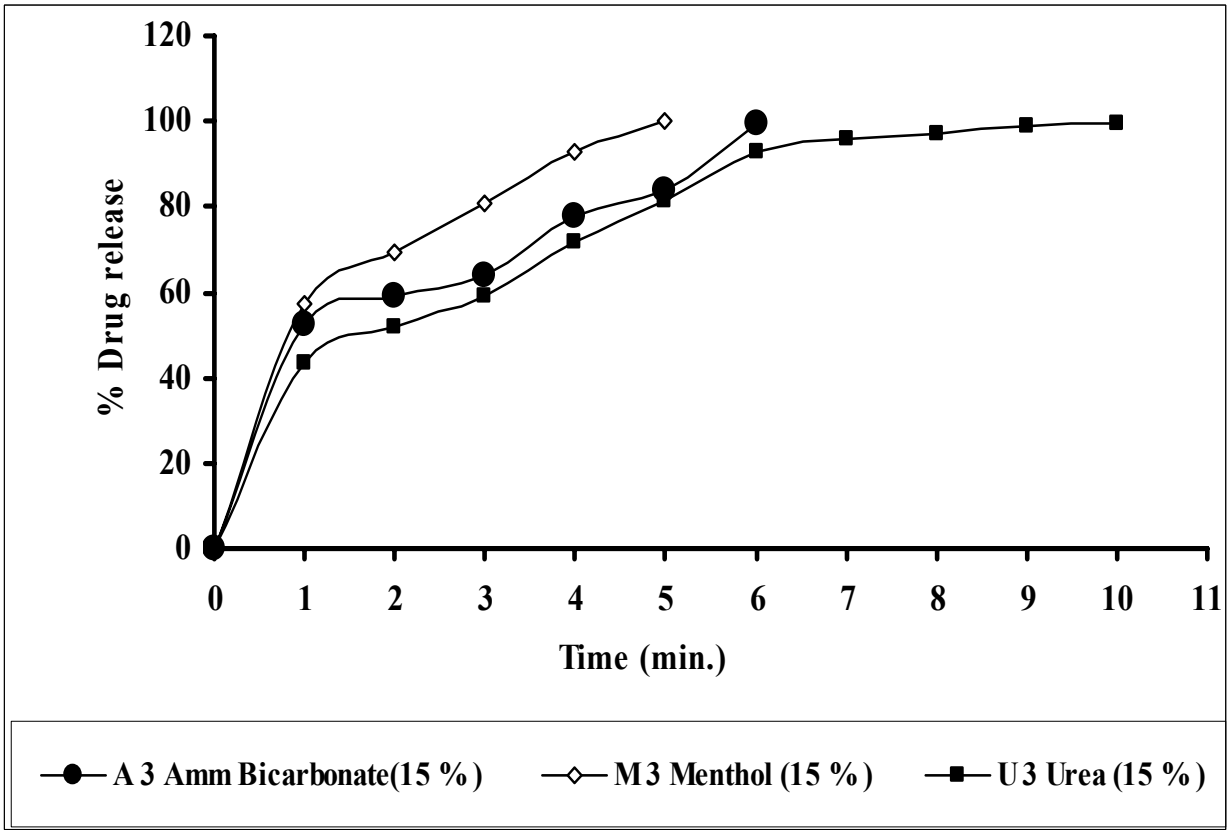

Fig 4: Dissolution profiles of best formulations prepared by using different subliming agent

dissolved in phosphate buffer pH 6.5 containing 0.1 % SLS. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV 1700 Shimadzu Corp., Japan) at 362 nm. Solubility studies of Felodipine in different solvents / buffer solutions were carried out to know the solubility of Felodipine and decide the appropriate dissolution medium. The solubility study results are compiled in **Table 3.**

In-vitro dissolution of Felodipine from tablets was carried out by using 900ml of phosphate buffer pH 6.5 containing 0.1 % SLS at 37 ± 0.5^0C and 50 rpm using programmable dissolution tester [paddle type, model TDT-OSL, Electrolabs,(USP), INDIA]. Aliquots were

Table 4: Pre-compressional parameters.

Form-ulation	Parameters		
	Angle of repose (θ) (± SD), n=3	Compressibility (%) (± SD), n=3	Hardness ratio (%) (± SD), n=3
A1	24.92 (0.72)	14.22 (1.22)	1.11 (0.04)
A2	22.17 (1.52)	14.12 (0.92)	1.37 (0.03)
A3	23.90 (1.37)	13.00 (0.12)	1.24 (0.02)
M1	24.58 (0.90)	14.48 (2.10)	1.32 (0.03)
M2	24.12 (1.22)	12.92 (1.10)	1.22 (0.05)
M3	25.17 (0.19)	15.00 (0.10)	1.37 (0.02)
U1	24.16 (0.55)	14.48 (1.22)	1.22 (0.06)
U2	25.79 (1.65)	14.34 (1.37)	1.38 (0.05)
U3	24.85 (2.10)	15.12 (1.59)	1.30 (0.01)

withdrawn at one minute time intervals and were replaced immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilution, were assayed spectrophotometrically (UV-1700, Shimadzu, Japan) at 362nm. The stability study of the tablets was carried out according to ICH guidelines by storing the tablets in stability chambers (Lab-care, Mumbai) at 40 ± 2^0C/75 ± 5% RH for three months.

Characterization of felodipine tablets:

FTIR Studies: IR spectra for drug, excipients and formulations A3, M3 and U3 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

RESULT AND DISCUSSION

Since, the flow properties of the powder mixture are important for the uniformity of mass of the tablets, the flow of the powder mixture was analyzed before compression to tablets. The values of pre-compression parameter evaluated were within prescribed limits as per USP XXVII and indicates a good free flowing property. The results are shown in **Table 4**. The post-compression parameters such as Hardness, friability, thickness, weight variation, disintegration time, wetting time, water absorption ratio, *in-vitro* dispersion time, drug content, $t_{50\%}$ and $t_{90\%}$ are shown **Table 5.** In all the formulations the hardness values indicates good mechanical strength and the hardness of the tablets decrease with increase in the amount of volatile component[14]. Friability of all formulations was less than 1%, which indicates that the tablets had a good

Table 5: Post compression parameters of tablets

Parameters	Formulations								
	A1	A2	A3	M1	M2	M3	U1	U2	U3
Hardness (kg/cm^2) ± SD, n=3	3.55 ± 0.10	3.50 ±0.15	3.30 ±0.09	3.60 ±0.05	3.50 ± 0.20	3.55 ± .19	3.00 ± 0.30	3.55 ± 0.05	3.30 ± 0.25
Friability (% w/w) ± SD, n=3	0.26 ± 0.04	0.30 ± 0.05	0.32 ±0.15	0.33 ± 0.02	0.26 ± 0.09	0.24 ±0.12	0.30 ± 0.02	0.51 ± 0.01	0.48 ± 0.07
Thickness (mm) ± SD, n=6	3.65 ± 0.05	3.25 ±0.07	3.50 ±0.02	3.75 0.09	3.34 ±0.01	3.33 ±0.02	3.62 ±0.03	3.68 ±0.03	3.70 ±0.07
Weight variation ± SD, n=10	151 ± 1.22	152 ±1.32	153 ±0.55	150 ± 0.75	152 ± 0.90	154 ± 1.10	156 ± 1.05	157 ± 0.85	155 ± 1.00
Wetting time (Sec) ± SD, n=6	35 ± 0.11	30 ± 0.06	18 ± 0.21	25 ± 0.09	20 ± 0.14	15 ± 0.07	50 ± 0.32	42 ± 0.15	30 ± 0.18
Water absorption ratio (%) ± SD, n=6	85.30 ± 0.19	82.37 ± 0.22	84.37 ±0.18	88.32 ± 0.24	83.33 ± 0.17	85.30 ± 0.21	84.24 ± 0.31	85.22 ± 0.44	88.30 ± 0.37
***In-vitro* dispersion time (Sec) ± SD, n=6**	35.20 ± 0.07	28.40 ± 0.05	15.20 ±0.04	30.30 ± 0.02	28.3 ± 0.05	14.02 ± 0.03	42.30 ± 0.02	40.00 ± 0.06	30.00 ± 0.04
Drug content (%) ± SD, n=6	102.00 ± 2.28	101.00 ± 1.27	99.27 ±1.87	105.10 ± 1.56	103.20 ± 0.99	100.00 ±0.87	102.00 ±1.12	101.34 ± 0.77	102.42 ± 1.55

Table 6: *In vitro* Dissolution parameters in phosphate buffer pH 6.5 containing 0.1% SLS

Formulation Code	Parameters					
	D_2	D_4	D_6	D_8	$T_{50\%}$	$T_{90\%}$
A3	59.19	77.95	99.40	--	0.95	5.43
M3	69.29	92.59	--	--	0.87	4.51
U3	51.71	71.69	93.12	97.03	1.73	9.03

A3 promising fast dissolving tablet containing 15 % ammonium bicarbonate as subliming agent, M3 promising fast dissolving tablet containing 15 % menthol as subliming agent, U3 fast dissolving tablet containing 15 % urea as subliming agent. D_2 is percent drug released in 2 min, D_4 is percent drug release in 4 min, D_6 is percent drug release in 6 min, D_8 percent drug release 8 min, $t_{50\%}$ is time for 50 % drug dissolution, $t_{90\%}$ is time for 90% drug dissolution.

mechanical strength. Drug content was found to be high (≥ 101.55 %) and uniform in all the formulations. The tablet thickness was found to be 3.25 to 3.75. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5 %, which provides good uniformity. The disintegration time of tablets decreased significantly with increase in the concentration of volatile substances.

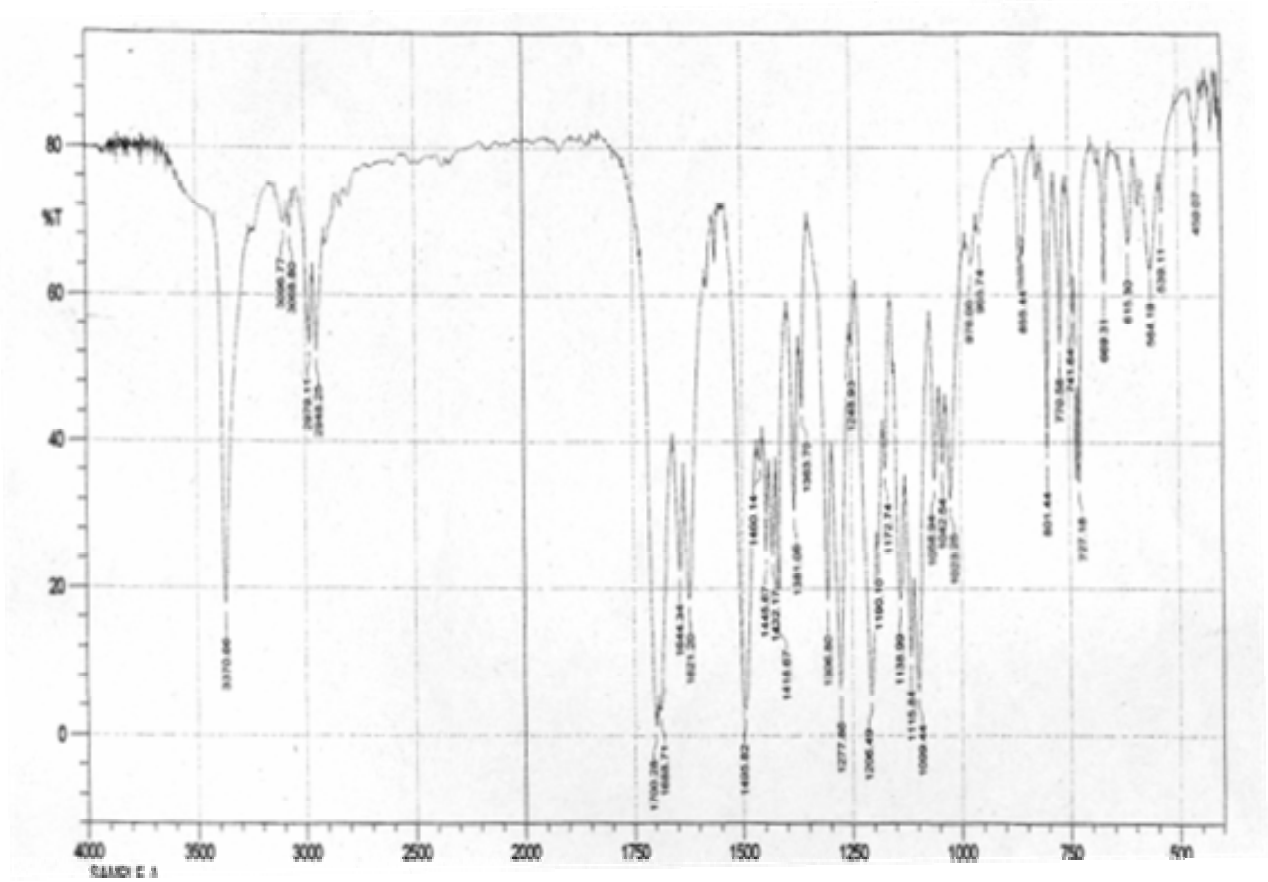

Fig 5: FTIR spectrum of felodipine

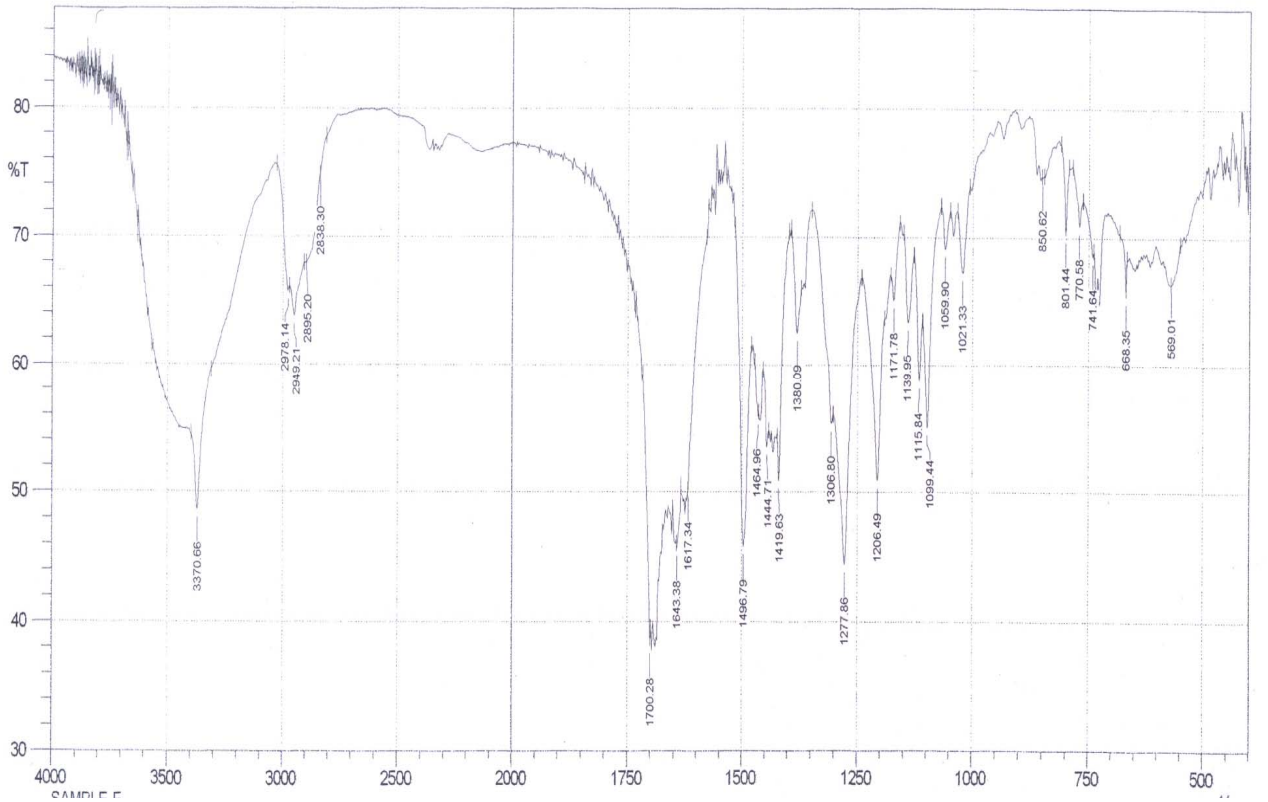

Fig 6: FTIR spectrum of formulation A3

The formulations containing micro crystalline cellulose as filler (A1-A3) showed minimum disintegration time this could be attributed towards disintegrating property of microcrystalline cellulose. However, the formulations containing mannitol as filler (U1-U3) showed longer disintegration time, which could be attributed to slower dissolution characteristics of mannitol[15]. Tablets prepared by vacuum drying technique rapidly exhibits high pores and disintegrates the tablets rapidly. It may be due to their lowest hardness and maximum porous structure was responsible for faster water uptake, hence it facilitates wicking action of crospovidone in bringing about faster disintegration[16].the wetting time of tablets also decrease with increase in the concentration of

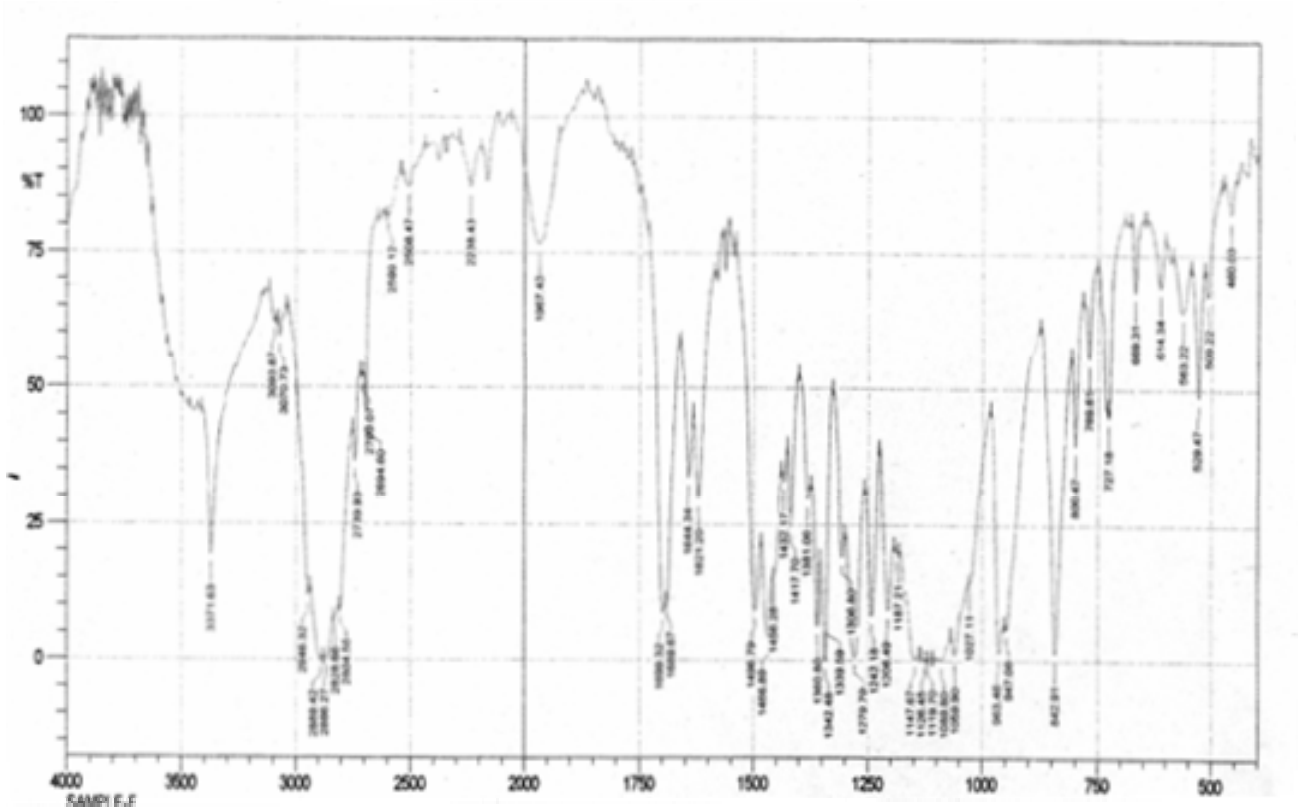

Fig 7: FTIR spectrum of formulation M3

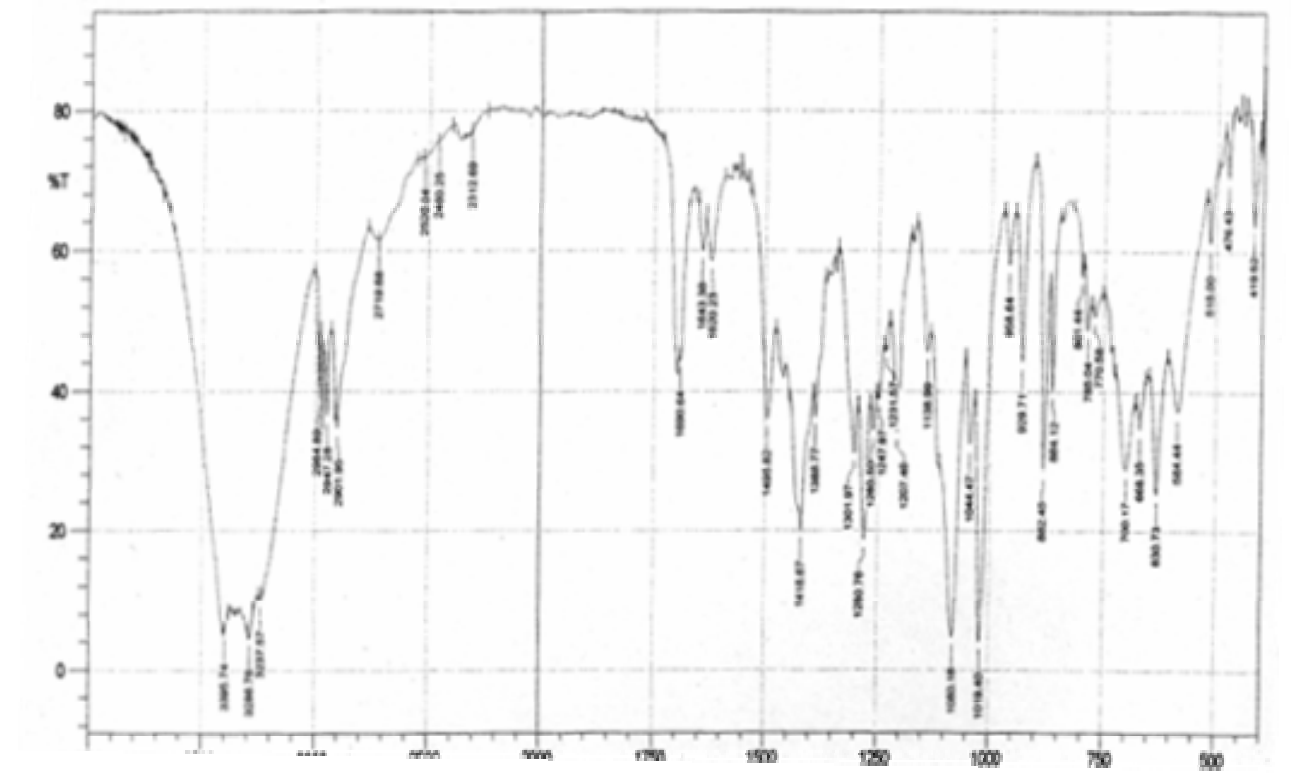

Fig 8: FTIR spectrum of formulation U3

volatile substances[16]. Water absorption ratio was found in the range 82.37 – 88.32 %, *in-vitro* dispersion time was found in the range 14.02 – 42.30s. The dissolution of felodipine from the tablets is shown in **Fig 1-3**. *In-vitro* dissolution studies on the promising formulation A3, M3, U3 formulations were carried out in pH 6.5 phosphate buffer containing 0.1 % SLS, and the various dissolution parameter values viz., percent drug dissolved in 2 min, 4 min, 6 min and 8 min (D_2, D_4, D_6, and D_8), $t_{50\%}$, and $t_{90\%}$ are shown in **Table 6**. This data reveals that overall, the formulation A3 and M3 shows nearly faster drug release. The formulations A3 and M3 50 % of drug released in 0.95 min, and 0.87 min respectively, and 90 % of drug released in 5.43 min, and 4.51 min respectively when compared to other tablet formulation. Dissolution of drug from tablets containing highest volatile substance and MCC as filler (A3and M3) were quicker than other formulations. It may be due to highest porosity, lowest hardness and disintegrating property of MCC, which leads to faster water uptake hence it facilitates wicking action of crospovidone in bringing about faster disintegration and dissolution. Dissolution profiles of best formulations prepared by using different subliming agents were shown in **Fig 4.**

The stability study for all the formulations were carried according to ICH guidelines by storing the tablets in a stability chamber (Labcare, Mumbai) at $40^o \pm 2^0$ C/ 75 ± 5% RH for three months. Decrease in the disintegration and the wetting time was observed in all the formulations, since during vacuum drying method tablets were exposed to only 6hrs at 80^0 C, where as 90 days and 45^0 C were used during stability studies. The long storage of 90 days at 45^0 C might have removed the trace amounts of volatile components, those were not removed during the short period bin vacuum drying method. There was no significant change in drug content of all the formulations **(Table 6)**.

In **[Fig 5]** shows the IR spectrum of the pure drug and formulations. The felodipine used in the present study shows characteristic absorption bands in the following IR region.

IR (KBR) cm^{-1}.

3370 (NH Stretching), 3069 (Aromatic CH stretching), 2840, 2948 (CH stretching of CH_2 and CH_3 Groups), 1700, 1688 (C=O stretching), 1644 (NH Bending), 1621, 1495, 1460 (C = C ring stretching), 1099 (C-O-C stretching), 727, 801 (Substituted benzene ring), 564 (Cl stretching).

The IR spectrum of the formulation A3 **[Fig 6]** shows the characteristic absorption bands in the following IR region. It is quite interesting to note that, the spectrum contains very broad peaks in the range 3200 to 3500 and a very sharp peak almost merged with the broad peak at 3370 indicating the presence of NH of Felodipine. The spectrum shows the presence of carbonyl group of drug at 1700 and 1688, NH bending 1643 and C=C ring stretching at 1617, 1496 and 1443. Since all the major peaks of the pure drug and excipients are present without any change in their positions in the spectrum of the formulation A3. It may be concluded that the drug and polymer have retained their identity without loosing their properties and not going in to a chemical interaction with each other. Thus the conclusion from the IR spectra of the drug and formulation is that there is no interaction between drug and polymer.

Similarly the IR spectra of formulations **[Figs 7, 8]** M3 and U3 reveal that the pure drug Felodipine has not gone into the interaction with menthol and urea in the formulation M3 and U3.

Table 6: Tablet parameters after stability studies.

Formulation	Dispersion time (sec) (± SD), n=6	Wetting time(sec) (± SD), n=6	Drug content (%)
A1	34.30 ± 0.04	31 ± 0.32	101.80 ± 1.12
A2	27.30 ± 0.03	27 ± 0.11	100.36 ± 0.92
A3	14.70 ± 0.02	16 ± 0.24	99.00 ± 1.18
M1	29.40 ± 0.03	21 ± 0.34	103.25 ± 0.92
M2	27.60 ± 0.04	18 ± 0.33	101.37 ± 2.22
M3	13.80 ± 0.02	10 ± 0.42	99.35 ± 1.38
U1	40.50 ± 0.03	48 ± 0.62	100.46 ± 1.35
U2	37.40 ± 0.07	38 ± 0.33	100.68 ± 0.92
U3	28.50 ± 0.07	24 ± 0.08	101.37 ± 1.10

CONCLUSION

The results of disintegration, time, wetting time and dissolution rate revealed that the amount of volatile component and type of filler significantly affect the dependent variables likes disintegration time, wetting time and dissolution rates. Thus it is concluded that fast disintegrating tablets can be prepared with a view of obtaining faster action of the drug and would be advantageous in compilations to the currently available conventional dosage forms. With the adopted vacuum drying technique an optimum point can be reached in the shortest time with minimum efforts and this technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of fast disintegrating tablets.

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