CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
https://doi.org/10.5281/zenodo.5730187

Available online at: http://www.iajps.com Research Article

FORMULATE ORO DISPERSIBLE TABLETS OF FELODIPINE FOR THE IMPROVEMENT OF SOLUBILITY, DISSOLUTION RATE AND ORAL BIOAVAILABILITY

[1] Chandra Sekhara Rao Baru and [2]Sushma Desai

[1,2] Faculty of Pharmacy, RGR Siddhanthi College of Pharmacy, Secunderabad, Telangana, India

Abstract:

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.

In the present work, an attempt has been made to develop fast disintegrating tablets of Felodipine. New generation super disintegrates Solutab, Explotab and Polyplasdone XL was selected as super disintegrates. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared

tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 110.4 % in 2 min hence it is considered as optimized formulation. The F4 formulation contains Solutab as super disintegrate in the concentration of 30 mg. F8 formulation also showed maximum percentage drug release i.e., 105.4% in 4 min ,it contains Explotab as super disintegrate in the concentration of 30 mg.

***Corresponding Author:**

Dr. Chandrasekhara Rao Baru,
Faculty of Pharmacy,
RGR Siddhanthi College of Pharmacy,
Secunderabad, Telangana, India

QR code

Please cite this article in press as Chandra Sekhara Rao Baru and Sushma Desai, ***Formulate Oro Dispersible Tablets Of Felodipine For The Improvement Of Solubility, Dissolution Rate And Oral Bioavailability****, Indo Am. J. P. Sci, 2018; 05(01).*

INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people [1].

Felodipine (4 RS)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1, 4-dihydropyridine-3,5-dicarboxylate is a calcium channel blocker used as antihypertensive and antianginal drug. [1,2] According to Biopharmaceutics Classification System, felodipine is class II drug, i.e., low solubility and high permeability. Felodipine has poor water solubility and hence poor dissolution and bioavailability after oral administration. Felodipine undergoes extensive first- pass metabolism with a bioavailability of about 15%.[3] The major drawback in the therapeutic application and efficacy of felodipine as oral dosage form is its low aqueous solubility, which is expressed to be approximately 19.17 mg/L at 25°C. Hence, improvement of its water solubility and dissolution is of therapeutic importance. [4,5

In the present work, an attempt has been made to develop fast disintegrating tablets of Felodipine. New generation super disintegrates Solutab, Explotab and Polyplasdone XL was selected as super disintegrates. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared
tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 110.4 % in 2 min hence it is considered as optimized formulation. The F4 formulation contains Solutab as super disintegrate in the concentration of 30 mg. F8 formulation also showed maximum percentage drug release i.e., 105.4% in 4 min ,it contains Explotab as super disintegrate in the concentration of 30 mg.

MATERIALS AND METHODS:

Materials Felodipine was obtained from Aurobindo Pharma, Hyderabad, Ac-Di-Sol, Primogel, Polyplasdone XL, Magnesium stearate, Talc and MCC pH 102 from Merk specialties Pvt Limited.

Determination of UV Absorption Maxima:

Felodipine solution was prepared in pH 6.8 phosphate buffer and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 265 nm.

Preparation Of Standard Calibration Curve of Felodipine:

100 mg of Felodipine was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with pH 6.8 phosphate buffer(pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with pH 6.8 phosphate buffer in 100ml to get 100µg/ml (working standard). Then 0.5, 1, 1.5, 2 and 2.5 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N Hcl to prepare 5µg, 10µg, 15µg, 20µg, and 25µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 265 nm against pH 6.8 phosphate buffer as blank. The absorbance was tabulated as in Table 5. Calibration curve was constructed and shown in Fig.1.

Tablet Formulation:

Formulation of Felodipine Dispersible Tablet by Direct- Compression:

Composition of preliminary trials for Felodipine Oro dispersible tablet by direct compression was shown in table 1. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 6mm flat punch, B tooling. Each tablet contains 10 mg Felodipine and other pharmaceutical ingredients.

Table 1: Formulation of Felodipine oro dispersible tablets

INGREDIENT	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F10	F11	F12
Felodipine	10	10	10	10	10	10	10	10	10	10	10	10
Ac-Di-Sol	2	4	6	8	-	-	-	-	-	-	-	
Primogel	-	-	-	-	2	4	6	8	-	-	-	-
PolyplasodneXL	-	-	-	-	-	-	-	-	2	4	6	8
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC pH102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation Parameters:
Precompression Parameters:

Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$D_b = M / V_b$$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$D_t = M / V_t$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder.

Angle of Repose (Θ):
The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan(\Theta) = h / r$$

$$\Theta = \tan^{-1} (h / r)$$

Where, Θ is the angle of repose.

h is the height in cm

r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 2: Angle of Repose as an Indication of Powder Flow Properties

S.No.	Angle of Repose(^{0})	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

Carr's index (or) % Compressibility:

It indicates powder flow properties. It is expressed in percentage and is give by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where,

Dt is the tapped density of the powder and

Db is the bulk density of the powder.

Table 3: Relationship between % compressibility and flow ability

S.No.	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very Poor
6	<40	Very Very Poor

Hausner Ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following

formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters:

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table No. 4.

Table 4: Weight Variation Specification as per IP

Average Weight of Tablets	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

In-Vitro Drug Release:

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800).

The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^{0}c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for famotidine by measuring absorbance at 265 nm.

For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8. Details:

Apparatus used : USP II Lab India DS 800
Dissolution Medium : Phosphate buffer PH 6.8
Dissolution Medium volume : 500ml
Temperature : 37^0C
Speed of paddle : 50rpm
Sampling Intervals : 2, 4, 6, 8, 10, 15, 20, 30min
Sample withdrawn : 5ml
Absorbance measured : 265 nm

Assay:
10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in pH 6.8 phosphate buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH 6.8. Absorbance was read at 265 nm against the reagent blank, and the concentrations of Felodipine in µg/ ml was determined by using the regression equation.

Concentration = absorbance/slope
Drug content in mg / tablet = conc. µg/ml * dilution factor
% Drug content = drug content in mg * 100 / label claim.

Drug- Excipient Compatibility Studies by FT-IR:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T).The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless-steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 8000 to 400cm^{-1}.

RESULTS AND DISCUSSION

Standard Calibration curve of Felodipine:

Table 5: Concentration and absorbance obtained for calibration curve of Felodipine in pH 6.8 phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance* (at 265 nm)
1	5	0.177
2	10	0.358
3	15	0.503
4	20	0.643
5	25	0.785

It was found that the estimation of Felodipine by UV spectrophotometric method at λ_{max} 224.0 nm in pH 6.8 phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5- 25µg/ml. The regression equation generated was y = 0.03x +0.042.

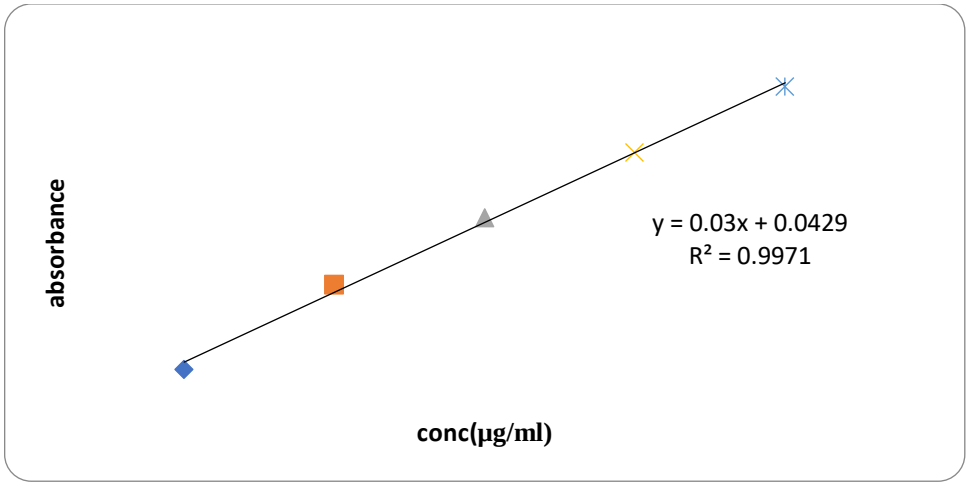

Fig 1: standard graph of Felodipine in pH 6.8 phosphate buffer

Evaluation Parameters for Fast Dissolving Tablets of Felodipine:

Pre-compression parameters:

The data's were shown in Table The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends was fall in the range of 13.79% to 18.64%. The Hausner ratio was fall in range of 1.16 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 6: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Ɵ)
F_1	0.45	0.55	18.18	1.22	27.91
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.50	0.58	13.79	1.16	29.34
F_4	0.46	0.55	16.36	1.19	26.71
F_5	0.50	0.58	13.79	1.16	29.34
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.50	0.58	13.79	1.16	29.34
F_8	0.41	0.50	18.34	1.21	26.78
F_9	0.48	0.56	18.02	1.21	26.78
F10	0.43	0.53	18.86	1.23	27.42
F11	0.48	0.59	18.64	1.22	25.85
F12	0.51	0.60	15	1.17	26.48

Post compression Parameters:

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7. The average weight of the tablet is approximately in range of 107 to 98.5, so the permissible limit is ±10% (110-90mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using monsanto hardness

Post-Compression parameters:

Tester and the data's were shown in above table.The results showed that the hardness of the tablets is in range of 2.5 to 3.00 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table. The result showed that thickness of the tablet 7.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table.The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro disintegration time:

Tablets of each batch were evaluated for in vitro disintegration time and the data's were shown in the Table.The results showed that the disintegration time of prepared tablets were in the range of 12.66 to 30.33 seconds.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 -99.25 %.

FD	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	105.6	2.5	3.59	20.33	0.43	97.23
F2	104.3	2.3	3.64	22.66	0.34	98.55
F3	99.6	2.5	3.59	30.33	0.49	98.16
F4	100.8	2.6	3.58	19.00	0.47	99.34
F5	98.4	2.3	3.59	20.33	0.49	98.16
F6	102.9	2.4	3.64	22.66	0.34	98.55
F7	101.4	2.5	3.59	25.33	0.49	98.16
F8	102.5	2.3	3.56	17.00	0.34	99.25
F9	97.5	2.5	3.56	21.00	0.34	99.25
F10	103.8	2.4	3.55	15.99	0.43	98.6
F11	102.4	2.2	3.45	19.00	0.54	98.7
F12	98.5	2.5	3.54	16.76	0.43	98.5

Table 7: Post-Compression parameters:

***In vitro* Dissolution studies:**

Invitro dissolution studies were carried out by using 500ml of 0.1 N HCl in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min.The dissolution data for all the formulations were given in the below table.

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
2	25.4	30.8	45.72	110.4	24.3	31.7	48.3	95.7	14.9	28.4	39.5	78.9
4	39.6	36.72	66.16	110.3	31.6	34.5	82.9	101.8	28.4	35.2	76.3	89.4
6	48.6	56.16	101.16		49.3	41.9	98.7		33.1	48.9	96.2	99.2
8	64.3	87.4			58.3	62.4			59.7	66.8	99.7	
10	76.4	98.5			74.3	89.1			79.3	78.1		
15	97.6				88.1	99.5			88.9	86.4		
20	97.1				94.6				93.5	100.3		
25					98.1				98.1			
30												

Table 8: *In vitro* dissolution data of Felodipine Oro dispersible Tablets

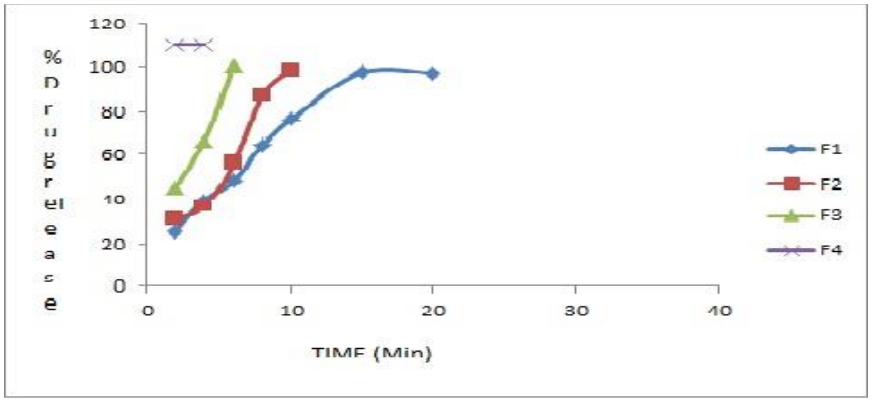

Fig 2: Dissolution profile of formulations prepared with Explotab as super disintegrate

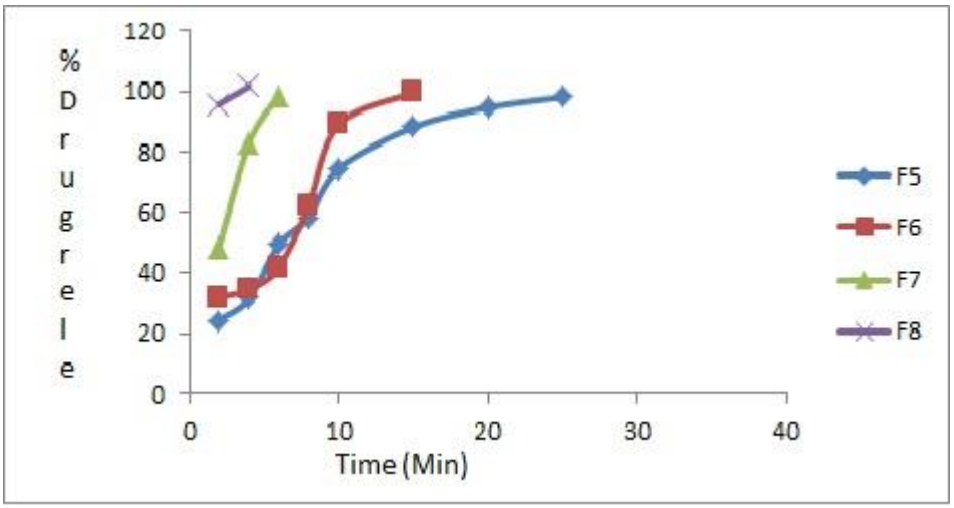

Fig 3 : Dissolution profile of formulations prepared with Polyplasdone XL as super disintegrate

From the tabular column it was evident that the formulations prepared with super disintegrate Solutab showed maximum % drug release in 2 min i.e.110.4% (F4 formulation and the concentration of super disintegrate is 30 mg).The formulations prepared with Explotab showed maximum percentage drug release in 4 min i.e., 105.4 % (F8 formulation and the concentration of super disintegrate is 30 mg).The formulation's prepared with Polyplasdone XL showed maximum percentage drug release in 6 min i.e.,99.2%.

Irrespective of super disintegrate type the disintegration time decreases and Dissolution time also decreases as the concentration of super disintegrate increases. The dissolution profile was represented in above graphs.

Fourier Transform-Infrared Spectroscopy:

From the FTIR data it was evident that the drug and super disintegrates, other excipients doses not have any interactions**.** Hence they were compatible.

CONCLUSION:

In the present work, an attempt has been made to develop fast disintegrating tablets of Felodipine. New generation super disintegrates Solutab, Explotab and Polyplasdone XL was selected as super disintegrates. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared
tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 110.4 % in 2 min hence it is considered as optimized formulation. The F4 formulation contains Solutab as super disintegrate in the concentration of 30 mg. F8 formulation also showed maximum percentage drug release i.e., 105.4% in 4 min, it contains Explotab as super disintegrate in the concentration of 30 mg.

REFERENCES:

1. Jianchen, X., Li, B., and Kang, Z., Taste masking microspheres for orally disintegrating tablets. *Int. J. Pharm.*, 359, 63-69 (2008).
2. Shukla, D., Subhashis, C., Sanjiv., Brahmeshwar, M., Mouth Dissolving Tablets II: An Overview of Evaluation Techniques. *Sci Pharm.*, 77, 327 – 341 (2009).
3. Sohi, H., Sultana, Y., Khar, R. K., Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. *Drug Dev. Ind. Pharm.*, 30, 429-448 (2004).
4. Puttewar, T., Kshirsagar, M., Chandewar, A. V., Chikhale, R., Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin. *J. K.Saud Univ.*, 22, 229–240 (2010).
5. Rakesh, P., Mona, P., Prabodh, C., Sharma., Dhirender, K., and Sanju, N., Orally Disintegrating Tablets – Friendly to Pediatrics and Geriatrics. *Arch. Pharm. Res.*, 2 (2), 35 – 48 (2010).
6. Suhas, M., Kakade., Vinodh, S., Mannur, Ketan., Ramani, B., Ayaz, A., Dhada., Chirag., Naval, V., Avinash, B., Formulation and Evaluation of

Mouth dissolving tablets of Losartan potassium by direct compression techniques. Int. J. Res. Pharm. Sci., 1(3), 290-295 (2010).

7. Suresh, B., Rajender, M., Ramesh, G., Madhusudan Rao, Y., Orodispersible tablets: An overview. *Asian J Pharm*., 2(1), 2-11 (2008).
8. Soumya.M*, Y.A.Chowdary, A.Madhuri, M.D.Sindhusha, T.Nagarani, B.Aruna, Manasa.V., Formulation And Invitroevaluation Of Fast Dissolving Tablets Of Flecainide Acetate . International Journal of Pharmacy and Pharmaceutical Sciences.,5(2),555-560(2013).
9. Tansel, C., Aysegul, D., Seluck, C., and Nursabah, B., Formulation and evaluation of diclofenac potassium fast-disintegrating tablets and their clinical application in migraine patients. *Drug Dev. Ind. Pharm.*, 37, 260-267 (2011).
10. Tejvir, K., Bhawandeep, G., Sandeep., and Guptha, G.D., Mouth Dissolving Tablets: A Novel Approach to Drug Delivery. *Int. J. Curr. Pharm. Res*., 3 (1), 1-7 (2011).
11. Uday, S., Rangole., Kawtikwar, P. S., and Sakarkar, D. M., Formulation and *Invitro* Evaluation of Rapidly Disintegrating Tablets using Hydrochlorothiazide as a model drug. *Research J. Pharm and Tech.*, 349 – 352 (2008).
12. William, R.P., Tapash, K., Orally disintegrating tablets. *Pharma. Tech.* (Product, Technologies and Development issues in Oct 2005).
13. Wipada, S., Praneet, O., Prasert, A., Tanasait, N., Kaewnapa, W., and Suwannee, P., Preparation and evaluation of taste-masked dextromethorphan oral disintegrating tablet. *Pharm. Dev. Technol*., 1-6 (2011).
14. Xiao, N., Jin, S., Xiaopeng, H., Wu, Y., Zhongtian, Y., Jihong, H., and Zhonggui, H., Strategies to improve dissolution and oral absorption of glimepiride tablets: solid dispersion versus micronization techniques. *Drug Dev. Ind. Pharm*., 1–10 (2010).
15. Xua, J., Bovet, L., Zhao, K., Taste masking microspheres for orally disintegrating tablets. *Int. J. Pharm.*, 359, 63–69 (2008).
16. Yourong, F., Shicheng, Y., Seong,J. H., Susumu, K., and Kinam, P., Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies. *Crit Rev Ther Drug Carrier Sys*., 21, 433–475 (2004).