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Formulation and Evaluation of Fast Dissolving Tablets of Felodipine

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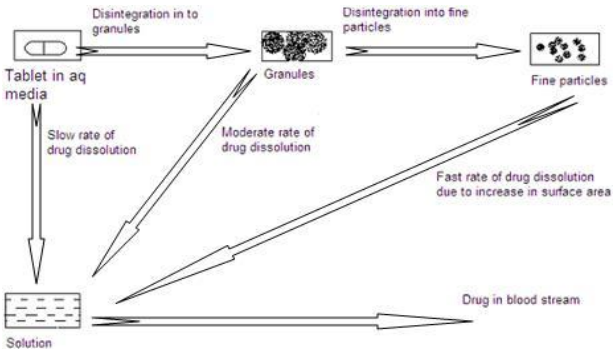
Abstract:-About 40% of new chemical entities (NCEs) are lipid soluble and are sparingly soluble in water. So inorder to increase their solubility, bioavailability and dispersibility of the drugs without affecting therapeutic activity of the drug the super disintegrants are used. Felodipine is a BCS class II drug with low solubility and high permeability for which the super disintegrant plantago ovata in the form of mucilage is used to enhance the disintegration,dispersibility and solubility.

I. INTRODUCTION

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physico- chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.The drug will dissolve at a slower rate from a non-disintegrating tablet due to exposure of limited surface area to the fluid. Disintegrating agents an important excipient of the tablet formulation, are always added to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.Disintegrating agent can be added either prior to granulation or prior to compression or at both the processing steps. Extragranular fraction of disintegrant (usually, 50% of total disintegrant requires) facilitates breakup of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles.



Schematic Representation Of Tablet Disintegration And Subsequent Drug Dissolution

Mechanism of tablet disintegration process:

The tablet gets disintegrated into small and fine particles by one or more mechanisms listed below:-

I.By capillary action
II.By swelling
III.Because of heat of wetting
IV.Due to disintegrating particle/particle repulsive forces
V.Due to deformation
VI.Due to release of gases
VII.By enzymatic action

II. TYPES OF DISINTEGRANTS

List Of Disintegrants

Disintegrants	Concentration	Inference
Starch USP	5-20	Higher amount is required, poorly compressible
Starch 1500	5-15	-
Pregelatinized starch	5-10	Lubricant properties and directly compressible
Solka floc(r)	5-15	Purified wood cellulose
Alginic acid	1-5	Acts by swelling
Na alginate	2.5-10	Acts by swelling
Polyplasdone(r)(XL)	0.5-5	Crosslinked PVP
Amberlite(r) (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Na CMC, HPMC	5-10	-
AC-Di-Sol(r)	1-3	Direct compression
	2-4	Wet granulation

Fast dissolving tablets are the need of the hour in the present generation as the people are being involved in too many schedules and also the availability of water is also being a problematic thing. so these tablets can be taken without water as they are designed to undergo pregastric absorption in the saliva bypassing the first pass effect. these tablets are advantageous to all group of people including paediatric and geriatric patients. so for better results use of super disintegrating agents may be used. some examples of commercially available fast dissolving tablets are :

Brand name	Active ingredient	Manufacturer
Felden fast melt	Piroxicam	Pfizer.Inc.,NY,USA
Maxalt MLT	Rizatriptin	Merck.Co.,NJ,USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea,New Delhi,India
Romilast	Montelukast	Ranbaxy lab Ltd, New Delhi, India
Pepcid RPD	Famotidine	Merck.Co.,NJ,USA

III. SUPERDISINTEGRANTS

As day's passes, demand for faster disintegrating formulation. is increased. So, pharmacist needs to formulate disintegrating agents i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

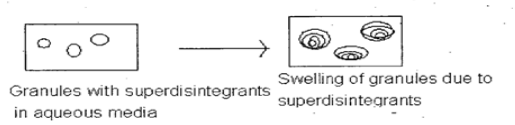


Fig. Mechanism of superdisintegrants by swelling

List Of Superdisintegrants

Superdisintegrants	Examples	Mechanism	Inference

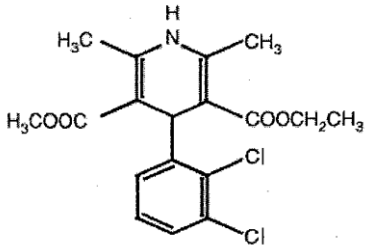
Crosscarmellose(r) Primellose(r) Solutab(r)	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M(r) Kollidon(r)	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab(r) Primogel(r)	Crosslinked starch	-Swells 7-12 folds in <30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine(r)	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy(r)	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritional products.
Calcium silicate		-Wicking action	-Highly porous, -light weight -optimum concentration is between 20-40%

Inspite of using super disintegrating agents we have to consider some other factors which may effect the disintegration process and the ultimate absorption and bioavailability of the tablet like the use of binder,lubricant,surfactant,etc. in the optimum and concentrations.

FELODIPINE:

Felodipine (Plendil) is a calcium antagonist (calcium channel blocker). Felodipine is a dihydropyridine derivative that is chemically described as + ethyl4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5 Pyridinedicarboxylate. It lowers blood pressure by reducing peripheral vascular resistance through a highly selective action on smooth muscle in arteriolar resistance vessels.

CHEMICAL STRUCTURE:



Empirical formula: $C_{18}H_{19}Cl_2NO_4$

Properties:

Felodipine is a slightly yellowish, crystalline powder with a molecular weight of 384.26. It is insoluble in water and is freely soluble in dichloromethane and ethanol. Felodipine is a racemic mixture. Its melting point is 145°C.

Category:

Antiarrhythmic agent

Antihypertensive agent
Calcium chaiihel blocker
Vasodilator agent

Mechanism of action:

Felodipine is a calcium channel blocker. It reversibly competes with nitrendipine and/or other calcium channel blockers for dihydropyridine binding sites, blocks voltage-dependant calcium currents in vascular smooth muscle and cultured rabbit atrial cells, and blocks potassium-induced contracture of the rat portal vein. By. blocking the calcium channels, felodipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes and result in a decrease of peripheral vascular resistance.

Pharmacokinetics:

Absorption: Felodipine is an orally administered drug and is almost completely absorbed and undergoes extensive first pass metabolism. The systemic bioavailability is approximately 20%. Mean peak concentration reaches in 2.5 - 5 hrs.

Distribution: The degree of plasma protein binding of felodipine is about 99%.

Half life: 14.1 hours

Bioavailability: 15 - 20

Metabolism: Felodipine has extensive hepatic first pass metabolism. Felodipine is metabolized by CYP3A4.

Storage: Store below 30°C (86°F). Keep container tightly closed. Protect from light.

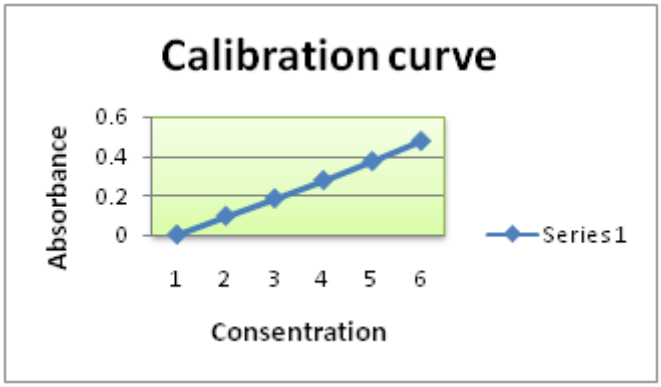
Adverse Reactions: The most common clinical adverse events reported peripheral oedema and headache. Rarely nausea , dyspepsia and constipation.

Objective:

Main objective of the work is to improve solubility of felodipine and to develop fast disintegrating tablets of felodipine using the natural super disintegrating agent plantago ovata in the form of mucilage (rather than the chemical or synthetic agents) to enhance the oral bioavailability and for faster onset of action.

Calibration curve for the estimation of felodipine in methanol

S.No	Concentration (µg/ml)	Absorbance
1.	0	0
2.	5	0.0943
3.	10	0.1825
4.	15	0.2750
5.	20	0.3711
6.	25	0.4729



Calibration curve for the estimation of felodipine in methanol

IV. DISCUSSION

The method obeyed Beer's law in the concentration range of 5-25 µg/ml. In order to find out degree of linear relationship correlation coefficient was calculated. It was found to be very near to I which indicates a high degree of correlation. Next it was of interest to establish the mathematical form of linear relationship between the two variables (concentration and absorbance) under consideration and the equation obtained was y = 0.0188x + 0.0022.

V. CONSTRUCTION OF CALIBRATION CURVE OF FELODIPINE

The calibration curve for felodipine was constructed using methanol and pH 6.8 phosphate buffer as solvents. The concentration maximum of felodipine in methanol was found to be 362 nm λ_{max} (Dong-Han Won et al) and Beer's law was. obeyed in the range of 5-25 µg/ml. An UV spectroscopic method based on measurement of absorbance at 362 nm was used for the estimation of felodipine.

VI. PREPARATION AND EVALUATION OF FASTDISINTEGRATING TABLETS OF FELODIPINE

In the present part of work, felodipine fast disintegrating tablets are prepared by direct compression method employing varying concentration of super disintegrant planatgo ovata mucilage. The prepared tablets are evaluated for physical characteristics and drug release studies.

Preparation of Felodipine Fast disintegrating Tablets

Different felodipine fast disintegrating tablets are prepared using varying concentration super disintegrant planatgo ovata mucilage.

VII. METHOD OF PREPARATION

l. The raw materials were passed through a screen (40 mesh) prior to mixing.

2. Then Powdered felodipne, was mixed with the other excipients

3. The mixture was then compressed on a tablet machine equipped Formulalor the preparation of fast disintegrating tablets of felodipine

Ingredients	POM 0%	POM 10%	POM 15%	POM 20%
Felodipine	10mg	10 mg	10 mg	10 mg
Planatgo ovata mucilage	0 mg	10 mg	15 mg	20 mg
Talc	2mg	2mg	2mg	2mg
Magnicium stearate	2mg	2mg	2mg	2mg
MCC	86 mg	76 mg	71 mg	66 mg
Total weight (mg)	100	100	100	100

Evaluation of Powder Properties of Tablet

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. The various characteristics of blends tested are as given below:

Angle of Repose

The angle of repose was determined by the funnel method suggested by Newman. Approximately 5gm of powder was poured through a glass funnel from a height of 6 centimeter onto a level bench top.The angle that the side of the conical heap made with the horizontal plane was recorded as the angle of repose.

Angle of repose is determined by the following formula

Tan θ@ = h/r

Where θ0 = Angle of repose

h and r are the height and radius of the powder cone.

Angle of. Repose(0)	Type of flow
<25	Excellent
25-30	Good
30-40	Fair/passable
>40	Very poor

2. Bulk Density

Aparent bulk density (pb) was determined by placing preseived drug excipients blend into a graduated cylinder and measuring the volume (Vb) and weight (M) " as it is."

pb = M/Vb

3. Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (pt) was calculated using following formula.

pt = M/Vb

Evaluation test for fast disitegrating tablets of felodipine

Weight variation

Twenty tablets from each batch were individually weighed individually on an analytical balance. The average weight and standard deviation were calculated and the results are shown in the table. Standard values are shown in the table given below.

Maximum % difference allowed	Average Weight of tablets (mg)	
	USP XXVU	IP 2007
10	130 or less	80 or less
7.5	130-324	80-250
5	More than 324	More than 250

Tablet hardness

Hardness of the tablet of each formulation was measured using Monsanto Hardness tester. One tablet from each batch were tested for hardness.

Friability

This test was performed using Roche friabilator. Three tablets were weighed and placed in the friabilator that revolves at a speed of 25 rpm, dropping those tablets at a) distance of 6 inches with each revolution.
The tablets were rotated in the friabilator for at least 4 minutes.

Friability apparatus

Friability is calculated by the formula

%loss in weight = (wl-w2/ wl) x 100

Where, w1= Initial weight of tablets before the test

w2 = Final weight of tablets after the test

In vitro disintegration time

In vitro disintegration time was performed by apparatus specified in USP at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as disintegration medium, and the temperature of which maintained at 37 ± 2°C and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds. Limits (IP 2007) all the tablets should disintegrate in less than 3 minutes.

Disintegration apparatus

Drug release studies

Drug release from different tablets was studied by carrying out the dissolution test in the following manner. The test was performed in Lab India dissolution test apparatus in 900m1 of pH 6.8 phosphate buffer and rpm of 75 by maintaining the temperature of the bath at 37 ± 0.5°C. Sink condition was maintained every time. Samples of 5m1 were taken and during each sampling replacement was made immediately with 5ml of the buffer solution.

Comparision of flow properties of different tablet blends

Properties	Angle of repose	Bulk density	Tapped density
POM (0%)			
POM (10%)	29.05	0.510	0.617
POM (15%)	28.56	0.501	0.609
POM (20%)	31.32	0.515	0.632

Flow Characteristics

It is a very well known that poorly flowing powders or granulations present several difficulties to the compression process. The values of pre-¬compression parameters evaluated (shown in table) are within prescribed limits and indicated good free flowing property. Angle of repose values between 23 and 30 show that the powder exhibited good flow properties.

Hardness, Friability and Weight variation of fast disintegrating Tablets

The hardness, friability and weight variation of formulated tablets are described in Table. To be acceptable by USP standards, the weight variation tolerance for uncoated tablets must be 7.5% or less. All the tablets have weight variation values within the limits. The friability obtained confirmed the suitability of direct compression technology to these powders. Good uniformity in drug content was found among different tablets.

Weight variation:

of SSG	Accepted variation	Actual weight	Weight variation
POM I	± 5	98	2
POM II	± 5	96	4
POM III	± 5	103	3
POM IV	± 5	101	1

Friability:

Percentage	Initial weight (3 tablets)	Final weight	% Error
0	296 mg	294 mg	0.68 %
10	300 mg	298 mg	0.67 %
15	306 mg	304 mg	0.65 %
20	302 mg	300 mg	0.66 %

Wetting time

This can be used as another confirmative test for the evaluation of fast disintegrating tablets, since the dissolution profiles of the tablets depend on the wetting followed by disintegration. Wetting times decreased with the .increasing levels of concentration of super disintegrants.

Disintegration time

The most important property that needs to be optimized in development of fast disintegrating tablets is the disintegration time of the tablets. In the present study all the tablets disintegrated in $\leq$ S 105 seconds. It was observed that the disintegration time of the tablets decreased as the concentration of POM increased.

Formulation	Disintegration time	Wetting time
SSG (0%)	92 seconds	111 seconds
SSG (10%)	60 seconds	91 seconds
SSG (15%)	52 seconds	62 seconds
SSG (20%)	45 seconds	50 seconds

Drug content:

Ten tablets were weighed and powdered, a quantity of powder equivalent to 1 mg of Felodipine was transfer-red to a 50 ml volumetric flask and 1ml methanol is added for solubilizing it better and volume is made upto 50 ml using pH 6.8 phosphate buffer is added. Then stoppered flask shaked vigorously for 15 minutes. then the liquid is filtered. The felodipine content was determined by measuring the absorbance at 362 nm after appropriate dilution with water. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Formulation	**Drug content%**
POM I	99.41%
POM II	98.87%
POM III	99.56%
POM IV	99.82%

VIII. DISSOLUTION STUDIES

The influence of super disintegrating agents on the dissolution profiles of felodipine fast disintegrating tablets are shown in the given table. T/z values decreased with the increase in the level of plantago ovata mucilage. As the concentration of disintegrating agent is increased, the dissolution rates increased.

Time in mins	%Release			
	POM I	POM II	POM	POM
0	0	0	0	0
5	35.17	45.34	57.27	65.82
10	46.87	56.23	70.97	78.16
15	70.56	72.79	85.76	92.39
20	87.22	89.45	91.12	94.26
30	91.13	91.32	-	-

IX. SUMMARY AND CONCLUSIONS

Many active pharmaceutical ingredients have excellent therapeutic efficacy but show poor oral bioavailability because of poor aqueous solubility. Pharmaceutical researchers use various techniques to overcome the problem of poor aqueous solubility and formulation of fast disintegrating tablets is one of the promising techniques available which is simple and effective. The current pharmaceutical research has drawn much attention on fast dissolving dosage forms due to their rapid onset of action and better acceptability among different age groups and other patients in emergency conditions. The main objective of this work is to improve solubility of felodipine and to develop fast dissolving tablets of felodipine using natural super disintegrating agents to enhance the oral bioavailability and for faster onset of action.

From the evaluation studies the following conclusions can be drawn

- The faster disintegration of tablets with plantago ovata mucilage may be attributed to its rapid capillary activity and pronounced hydration.
- The dissolution studies showed a initial rapid release (in first 5 minutes), followed by a slow and steady release later.
- The dissolution rate followed first order kinetics.
- T50 values decreased with the increase in.the level of plantago ovata mucilage concentrations..

In the present part of the work, effect of super disintegrant in varying concentrations on the drug release of felodipine from tablets was evaluated. Four different formulations of felodipine were prepared by direct compression method employing varying concentrations of super disintegrant (plantago ovata mucilage). These tablets were evaluated for hardness , friability, weight variation, disintegration time , wetting time , drug content and drug release studies.

1 All the formulations exhibited good hardness, friability and weight variation. The drug content uniformity of all the tablets is also within the limits.

2. The formulations POM 3 and POM 4 showed faster disintegration and wetting time compared to other formulations.Thus the results indicated that the dissolution profiles of the tablets are in agreement with the disintegration time values observed. All the tablets disintegrated in less than 3 minutes. Thus the objective of preparing fast disintegrating tablets is achieved.

X. CONCLUSION

It is concluded that fast dissolving tablets of felodipine prepared with 20 % of super disintegrant showed decrease in disintegration time, wetting time and dissolution time and we estimate that this formulation is the best among the other formulations which contain a lesser concentration of super disintegrant.

XI. SCOPE FOR FURTHER WORK

An attempt may be made to improve the disintegration of other poorly soluble drugs. An attempt may be done to improve the solubility of insoluble drugs. Other such methods to improve dissolution characteristics are complexation with complexing agents and size reduction, use of surfactants. By the formulation of the disintegrating tablets, bioavailability of the drug can be increased to a remarkable extent.

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