

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 in order to increase their solubility super disintegrates are used. Drugs are generally classified into highly permeable and highly soluble - type 1, highly permeable and low soluble - type 2, low permeable _ and highly soluble - type 3, low soluble and low permeable - type-4 . In order to increase the bioavailability and dispersibility of the drugs super disintegrants are used. They generally increase the bioavailability of the drug and they does not affect the therapeutic dose of the drug.

Introduction:

Boavailability 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 physical - 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. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration. Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with. aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

Methods of Addition of Disintegrates

The method of addition of disintegrants is also a crucial part. Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at the both 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.

TYPES OF DISINTEGRANTS

Starch

Starch was the first disintegrating agent widely used in tablet manufacturing. Before 1906 potato starch and corn starch were used as disintegrants in tablet formulation. However, native starches have certain limitations and have been replaced by certain modified starches with specialized characteristics. The mechanism of action of starch is wicking and restoration of deformed starch particles on contact with aqueous fluid and in doing so release ,of certain amount of stress which is responsible for disruption of hydrogen bonding formed during compression. Lowenthal & Wood proved that the rupture of the surface of a tablet employing starch as disintegrant occurs where starch agglomerates were found.

The conditions best suited for rapid tablet disintegration are sufficient number of starch agglomerates, low compressive pressure and the presence of water. The concentration of starch used is also very crucial part. If it is below the optimum concentration then there are insufficient channels for capillary action and if it is above optimum concentration then it will be difficult to compress the tablet.

Pregelatinized Starch

Pregelatinized starch is produced by the hydrolyzing and rupturing of the starch grain. It is a directly compressible disintegrants and its optimum concentration is 5-10%. The main mechanism of action of Pregelatinized starch is through swelling.

Modified starch

To have a high swelling properties and faster disintegration, starch is modified by carboxy methylation followed by cross linking, which is available in market as cross linked starch. One of them is SODIUM STARCH GLYCOLATE. Even low and substituted carboxymethyl starches are also marketed as Explotab Primojel®. Mechanism of action of this modified starches are rapid and extensive swelling with minimum, gelling. And its optimum concentration is 4-6 %. If it goes beyond its limit, then it produces viscous and gelatinous mass which increases the disintegration time by resisting the breakup of tablet. They are highly efficient at low concentration because of their greater swelling capacity.

Cellulose and its Derivatives

Sodium carboxy methylcellulose (NaCMC and CARMELLOSE sodium) has highly hydrophilic structure and is soluble in water. But when it is modified by internally crosslinking we get modified crosslinked cellulose i.e. Crosscarmellose sodium which is nearly water insoluble due to cross linking. It rapidly swells to 4-8 times its original volume when it comes in contact with water.

Microcrystalline Cellulose (MCC)

MCC exhibit very good disintegrating properties because MCC is insoluble and act by wicking action. The moisture breaks the hydrogen bonding between adjacent bundles of MCC. It also serves as an excellent binder and has a tendency to develop static charges in the presence of excessive moisture content. Therefore, sometimes it causes separation in granulation. This can be partially overcome by drying the cellulose to remove the moisture.

Alginates

Alginates are hydrophilic colloidal substances which has high sorption capacity. Chemically, they are alginic acid and salts of alginic acid. Alginic acid is insoluble in water, slightly acidic in reaction. Hence, it should be used in only acidic or neutral granulation. Unlike starch and MCC, alginates do not retard flow and can be successfully used with ascorbic acid, multivitamin formulations and acid salts of organic bases.

Ion-exchange resin

Ion exchange, resin (AmbreliteRIPR-88) has highest water uptake capacity than other disintegrating agents like starch and Sodium CMC. It has tendency to adsorb certain drugs.

Miscellaneous

This miscellaneous category includes disintegrants like surfactants, gas producing disintegrants and hydrous aluminium silicate. GAS PRODUCING DISINTEGRATING AGENTS IS used in soluble tablet, dispersible tablet and effervescent tablet. Polyplasdone®XL and Polyplasdone®XL10 act by wicking, swelling and possibly some deformation recovery. Polyplasdone®XL do not reduce tablet hardness, provide rapid disintegration and unproved dissolution. Polyplasdone® as disintegrating agent has small particle size distributions that impart a smooth mouth feel to dissolve quickly. Chewable tablet does not require addition of disintegrant.

SUPERDISINTEGRANTS

As day's passes, demand for faster disintegrating formulation. is increased. So, pharmacist needs to formulate disintegrants 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.

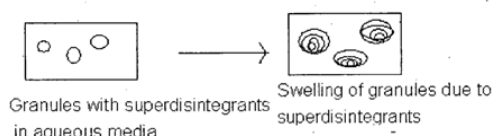


Fig. Mechanism of superdisintegrants by swelling

FACTORS AFFECTING DISINTEGRATION

The solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Chebli and cartilier proved that tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to its amorphous character and has no solid planes on which the disintegrating forces can be exerted than the tablet made with crystalline lactose monohydrate.

Effect of binder

As binding capacity of the binder increases, disintegrating time of tablet increases and this counteract the rapid disintegration.

Even the concentration of the binder can also affect the disintegration time of tablet.

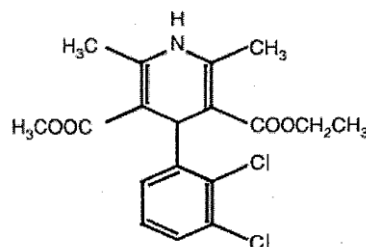
Effect of lubricants

Mostly lubricants are hydrophobic . and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other 13 particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration. Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants. On the contrary, the disintegration time is hardly affected if there is some strongly swelling disintegrants are present in the tablet. But there is one exception like sodium starch glycolate whose effect remains unaffected in the presence of hydrophobic lubricant unlike other disintegrants.

FELODIPINE:

Felodipine (Plendil) is a calcium antagonist (calcium channel blocker). Felodipine is a dihydropyridine derivative that is chemically described as + ethyl 4-(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 channel 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.

Drug Interactions : Care must be taken when felodipine is co-administered with CYP3A4 inhibitors (eg: Ketoconazole, itraconazole, erythromycin, grape fruit juice, cimetidine) because it may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism.

Beta-blocking agents: A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significance effects on the pharmacokinetics of felodipine. The AUC and Cmax of metoprolol , however , were increased approximately 31 and 38 % , respectively. In controlled clinical trials, however., beta blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

CYP3A4 inhibitors: Felodipine is metabolized by CYP3A4. Co-administration of CYP3A4 inhibitors (eg : ketoconazole, itraconazole, erythromycin, grapefruit juice , cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine , either due to an increase in bioavailability or due to decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with co administration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are co-administered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole : Co-administration of another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6- fold increase in the Cmax, and 2-fold prolongation in the half life of felodipine.

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.

AIM OF WORK

To formulate fast dissolving tablets of felodipine to decrease the disintegration time and to increase its bioavailability. There by increasing the onset of action of felodipine at its therapeutic dose and to decrease the patient compliance.

PLAN OF WORK

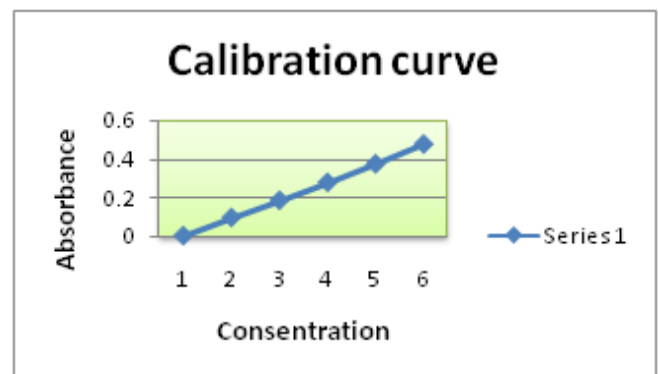
Main objective of the work is to improve solubility of felodipine and to develop fast disintegrating tablets of felodipine to enhance the oral bioavailability and for faster onset of action.

PLAN OF WORK

1. Construction of calibration curve of felodipine
2. Preparation and evaluation of fast disintegrating tablets of felodipine
 - Preparation of Felodipine fast disintegrating tablets
 - Evaluation of Felodipine fast disintegrating tablets.
 - Powder flow properties (Angle of repose)
 - Hardness and friability
 - Disintegration time
 - Dissolution time
 - Wetting time.

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

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 1 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 $y = 0.0188x + 0.0022$.

CONSTRUCTION OF CALIBRATION CURVE OF FELODIPINE

The calibration curve for felodipine was constructed using methanol as a solvent. The objective of the study was to develop simple, rapid, accurate and specific spectrophotometric method for the estimation of felodipine using spectrophotometry. The simple method was developed using solvent distilled water with minimum processing steps. The λ_{max} of felodipine in methanol was found to be 362 nm (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.

Materials

1. Felodipine
2. Methanol (Qualigens)

Stock solution

100mg of felodipine was accurately weighed and transferred into a 100ml volumetric flask. The volume was made upto 100ml with methanol to obtain a stock solution containing 1 mg/ml concentration.

Sub-stock solution

5ml of stock solution was taken in a 100ml volumetric flask and the volume made up to 100ml with methanol- to obtain a sub stock solution containing 50µg/ml concentration.

PREPARATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF FELODIPINE

In the present part of work, felodipine fast disintegrating tablets are prepared by direct compression method employing varying concentration of super disintegrants like 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 disintegrants like planatgo ovata mucilage.

Method of preparation

1. 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

$$\text{Tan } \theta = h/r$$

Where θ = Angle of repose

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

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

2. Bulk Density

Apparent bulk density (p_b) was determined by placing pre-weighed drug excipients blend into a graduated cylinder and measuring the volume (V_b) and weight (M) " as it is."

$$p_b = M/V_b$$

3. Tapped density

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

$$p_t = M/V_b$$

Evaluation test for fast disintegrating 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

$$\% \text{ loss in weight} = (w_1 - w_2 / w_1) \times 100$$

Where, w_1 = Initial weight of tablets before the test

w_2 = 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 $37 \pm 2^\circ\text{C}$ 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 500ml of 1.0 N HCl and rpm of 75 by maintaining the temperature of the bath at $37 \pm 0.5^\circ\text{C}$. Dissolution was carried out in 500ml of 0.1N HCl. Sink condition was maintained every time. The samples were withdrawn by replacing the sampled dissolution media with the buffer solution. Samples of 5ml were taken during each sampling time and the replacement was made immediately with 5ml of the buffer solution.

Comparison 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

Experimental Work:

Materials and methods

Materials:

- Felodipine (active constituent)
- Plantago ovata mucilage (main super disintegrant)
- Talc
- Magnesium stearate
- Micro crystalline cellulose

Equipment:

- Digital balance
- Sieves (40mesh)
- Blender
- Single punch tablet compressor
- Friability apparatus
- Disintegration apparatus
- Dissolution, apparatus

Methods:

1. Wet granulation method:

Wet granulation is a process of using a liquid binder to lightly agglomerate the

powder mixture. The amount of liquid has to be properly controlled, as over-

wetting will cause the granules to be too hard and under-wetting will cause them

to be too soft and friable. Aqueous solutions have the advantage of being safer to

deal with than solvent-based systems.

- Procedure
 - Step 1: The active ingredient and excipients are weighed and mixed.
 - Step 2: The wet granulate is prepared by adding the liquid binder-adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cellulose derivatives such as methyl cellulose.
 - Step 3: Screening the damp mass through a mesh to form pellets or granules.
 - Step 4: Drying the granulation. A conventional tray-dryer or fluid-bed dryer, hot air oven are most commonly used.
 - Step 5: After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process.

Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process.

2. Dry granulation method

Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation. Dry granulation is simpler than wet granulation, therefore the cost is reduced. However, dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules.

Results and discussion

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.

Dissolution Studies:

The influence of super disintegrants 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 isintegrant increased, the dissolution rates increased.

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 super disintegrants 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 wet granulation and 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.

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.

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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