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Formulation and Evaluation of Fast Dissolving Tablet of Nifedipine

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HUMAN

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ABSTRACT

In the present study, there was an attempt to make rapidly dissolving tablets using the direct dissolution method containing Nifedipine-Mannitol solid dispersion. The main objective of the work was to prepare nifedipine solid dispersion with Mannitol to initiate action. The solid dispersion was prepared by the solvent evaporation method and evaluated for cumulative drug release. FDT was formulated by a direct compression method using different super Disintegrants such as CCS and SSG in different ranges (1–3 %). Preformation studies were performed on the powder mixture for tablets. The flow properties (F1 – F18) of the mixture were evaluated by determining the Carr's index, the Hausner ratio, and the angle of view. Condensate density, tapped density, Carr's index, Hausner ratio and representation of angles. The formulated tablets were evaluated for thickness, hardness, stability, weight variation, wetting time, drug content uniformity, dissolution time, and in-vitro dissolution studies. Thus it was concluded that FDT with Nifedipine-Mannitol solid dispersion with reduced dissolution time can be prepared by direct compression method using a co-processed mixture of cross carmellose sodium and sodium starch Glycolate in the ratio 1% and 2% as superdisintegrants respectively.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely used route of administration among all routes that have been traced to systemic delivery of drugs through various pharmaceutical products of different dosage forms.[1]

Solid dosage forms are popular due to ease of administration, precise dosage, self-medication, pain relief, and most importantly patient compliance. The most popular solid dosage forms are pills and capsules. An important drawback of these dosage forms for some patients however is difficulty in swallowing.[2]

Recent developments in technology have presented viable dosage options for patients who may have difficulty swallowing pills or capsules. Traditional tablets and capsules administered with water may be inconvenient or impractical for other patients. In such situations rapidly disintegrating / dissolving tablets are required which can be administered without water. Such rapid dissolving/dissolving pills (FDT) spread rapidly after mixing in saliva to form a suspension or solution of the drug that is easily swallowed by patients.[3]

The target population for these new rapidly dissolving dosage forms has typically been pediatric, geriatric and bed rested or developmentally disabled patients. Persistent nausea patients who are traveling or who have little or no access to water are also good candidates for rapidly dissolving pills. Pharmaceutical marketing is another reason for the increase in available rapidly dissolving / dissolving products[6]. The major advantage of FDT is that it combines the benefits of both liquid and traditional tablet formulations, providing benefits over both traditional dosage forms.[7]

Some FDTs also claim an increased bioavailability compared to conventional tablets because of pre-gastric absorption due to diffusion in saliva[8]. Rapidly dissolving drug delivery systems have started gaining popularity and acceptance as new delivery systems, as they are easier to manage and lead to better patient compliance. However, for the elderly and infants, traditional pills present some difficulties when consumed, usually, elderly patients experience difficulty swallowing the traditional dosage forms (tablets, capsules, solutions and suspensions), as in extremities, dysphagia and due to the tremor of additional pyramidal disorders such as parkinsonism. In such cases, priority will be given to liquid dosage forms, which also have their own disadvantages.

FDT has additional advantages over both solid and liquid forms. Apart from this, it is the best way of administering the medicine for the mentally ill, disabled and uncooperative person. The bulk of pharmaceutical research is focused on the development of these rapidly dissolving delivery systems.[9]

- **IDEAL CHARACTERISTICS OFFDTs:**

- They should not require water or other liquid at the time of administration.

- They should easily disintegrate or dissolve in oral cavity.

- They should allow high drug loading.

- They should have pleasant mouthfeel.

- They should haven eligible or no residue in the oral cavity after administration as whole drug passes to GIT.

- They should show low sensitivity against environmental conditions i.e. moisture, temperature etc.

- **SIGNIFICANCE/ADVANTAGES OF FDTs:**

- FDTs offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include:

- There is no risk of interruption in dosage form, which is beneficial for traveling patients who do not have access to water.

- Easy to administer for paediatric, geriatric and institutional patients (especially for mentally retarded and psychiatric patients).

- Rapid disintegration of the pellet as a result of accelerated dissolution and rapid absorption, providing a rapid onset of action.

- Excellent mouth feels property created by the use of taste and sweetness which has changed the concept of medicine as a "bitter pill".

- Increased bioavailability of drugs absorbed by the mouth, pharynx and oesophagus.

- Reduction in dose and increase in bioavailability due to pregastric absorption of drugs that avoid liver metabolism.[4]

- **CHALLENGES TO DEVELOP FDTs**:

- Achieving rapid dissolution of the tablet.

- Avoid increasing the size of the tablet.

- Adequate mechanical strength.

- Do not leave minimal or no residue in the mouth.

- Protection from moisture.

- Good package design.

- Compatible with flavour masking techniques.

- Not affected by drug properties.

- **FORMULATION ASPECTS IN DEVELOPINGFDTs:**

The challenges faced by researchers in the development of FDTs are to produce the tablet with sufficient mechanical strength, which disintegrates rapidly in the mouth. The tablets should have an acceptable taste and leave little or no residue in the mouth. Orally disintegrating pills are made using a number of procedures, which differ in their functioning. These differ from the conventional tablets in properties such as-

- Mechanical strength of tablets.

- Taste and touch mouth.

- Swallowing ability.

- Rate of drug dissolution in saliva.

- Rate of absorption from saliva solution.

- Drug and dosage form stability.

- **DRUGS EXPLORED FOR FDTs:**

The following category of drugs can be considered to be formulated as FDTs: Analgesics, Anaesthetics, Antianginal, Anticonvulsants, Antipyretics, Anti-inflammatory, Antibiotics, Antihistaminic, Antispasmodic, Antiasthmatics, Diuretics, Antiarrhythmic, Antimigraine, Antipsychotics, Antiulceretive, and Antivenin Bronchodilator etc.

- **TECHNIQUES USED IN THE PREPARATION OF FDTs:**

Various techniques used in formulating FDTs include:

- **Freeze Drying:** Lyophilisation/Freeze drying there is a pharmaceutical technique, which allows heat sensitive drugs and organic materials to be dried at low temperatures, which allow water to be removed by sublimation.

- **Cotton Candy Process:** The process is named so because it uses a unique spinning mechanism to mimic a floss-like crystalline structure, which mimics cotton candy. The cotton candy process involves the creation of a matrix of polysaccharides or saccharides by the simultaneous action of flash melting and spinning.

- **Moulding/Moulding:** In this method, the ingredients are moistened with a hydro-alcohol solvent and the moist mixture is compressed into tablets using low compression forces. The solvent inside the tablets is removed by air drying. The molded tablets so formed have a porous structure, which increases the dissolution and dissolution rate of the product.

- **Spray-drying:** Highly porous and finer powders can be produced by the spray drying process as the processing solvent rapidly evaporates during spray drying. It can be used to prepare FDT.

- **Mass-extrusion:** The technique involves softening the active mixture with a solvent mixture of water-soluble polyethylene glycol (PEG) using a heated blade to form a tablet of a product using a mass of softener through an extruder or syringe. Can also be obtained in segments.

- **Sublimation:** Due to low porosity, compressed tablets composed of highly water-soluble excipients as matrix materials often do not rapidly dissolve in water. Porous tablets that exhibit good mechanical strength and dissolve quickly, have been developed using inert

volatile solid ingredients such as urethane, ammonium carbonate, camphor, naphthalene, etc. The porous was achieved by introducing volatile material.

- **Direct Compression:** The use of conventional equipment, commonly available excipients and a limited number of processing steps in direct compression makes this the easiest process to manufacture FDTs. High doses can be accommodated and final weight of the tablet can easily exceed that of other production methods.

- **PATENTED TECHNOLOGIES OF FAST DISSOLVING DRUG DELIVERY SYSTEM:** Technology tablet patented by R.P. Scherer. The Zydis Formulation is a unique freeze-dried tablet, consisting of a physical mesh of the drug in a matrix, composed of a saccharide and a polymer.

- **Shear form technology/flash dose Technology:** The technique is based on the preparation of floss, also known as shear matrix, which is subjected to a feedstock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to a centrifugal force and a temperature gradient, which raises the temperature of the mass to create an internal flow condition, which allows it to move with respect to the mass. The flowing mass exits through the spines which flow the floss. The floss produced at such a high volume is amorphous in nature, sliced and reorganized by various techniques to provide uniform flow properties and thus facilitate blending. The re-crystallized matrix is mixed with the active ingredient and other tablet excipients and compacted into tablets. The active material and other excipients may be mixed with the floss before carrying out recrystallization.

- **Ceform Technology:** In the Ceform technique, microspheres with active drug content are prepared. The essence of the manufacturing process of Ceform microspheres is a dry powder containing sufficiently pure pharmaceutical material or a particular mixture of pharmaceutical ingredients plus other pharmaceutical compounds and excipients in a precision engineered and rapid spinning machine. The centrifugal force of the rotating head of the Ceform machine throws the dry drug mixture at high speeds through small, hot openings. The carefully controlled temperature of the resulting microburst of heat mixes to form a sphere without adversely affecting drug stability. Microspheres are then compressed into mixed and / or preselected oral delivery dosage formats. The ability to process both the drug and excipients simultaneously produces a unique microenvironment in which the

material can be incorporated into microspheres that can alter the characteristics of the drug substance, such as enhancing solubility and stability. Microspheres can be included in a wide range of FDTs such as flash doses, EZchew, spoon doses as well as traditional tablets.

- **Durasolv Technology:** This technology is patented by CIMA labs. The tablets produced by this technique use conventional tableting devices and have good hardness (less than 2% stability). Pills are made using medicine, non-direct compression filler and lubricants. The tablets obtained are strong and can be packed in bottles and blisters in conventional packing. Nondirect compressed filler is commonly used in the range of 60–95% and lubricants in the range of 1-2.5%. Durasolv is a suitable technique for products requiring low amounts of active ingredients.

- **Orosolv Technology:** Orosolv technology developed by CIMA labs Makes tablets that contain flavor masked active ingredients and waste agents that rapidly decompose when exposed to saliva and release flavor masking radiant. The tablets are made by direct compression techniques at low compression force to reduce oral dissolution time. Traditional blender and tablet machines are used to produce tablets. The pills produced are soft and friable and packaged in a specially designed pick and place system. Orosolv formulations are not very hygroscopic.

- **Wow tab Technology:** Wow tab technology is patented by Yamanouchi pharmaceutical company. WOW means without water". In this process, a combination of low mould potential saccharides (rapid dissolution) and high mould potential saccharides (good binding properties) is used to obtain a strong melting fast pellet. The active ingredient is mixed with low mould potential saccharides (such as lactose, glucose, sucrose, Mannitol, etc.) and granulated with a high mould capacity saccharide (such as maltose, sorbitol, and oligosaccharide) and compressed into tablets. The ratio of high mould capacity saccharide to the low mould capacity saccharide used is 2–20% by weight. Active ingredients can be used in 20 - 50% w / w tablet amounts.

- **Flash tab Technology**: Prographarm Laboratories has patented the Flash Tab technology. Tablets prepared by this system have an active ingredient in the form of microcrystals. Drug micro granules can be prepared using traditional techniques such as co-preservation, microencapsulation and simple pan coating method. All processing uses

traditional tabulating technology and the produced tablets have good mechanical strength with short dissolution time.

- **Ora quick Technology:** KV Pharmaceuticals has patented this technology. It uses the Taste Masking Microsphere technology termed as Micro Mask, which provides better mouthfeel, significant mechanical strength and quick dissolution/dissolution of the product. This process involves the preparation of microscopic particles in the form of drug-protecting matrices, which can be compressed with sufficient mechanical strength. The low heat produced in this process makes it suitable for heat sensitive drugs. The Ora instant product dissolves within a few seconds.

- **Dispersible Tablet Technology**: This technology patented by Lek, produces FDTs with the dissolution rate is improved by incorporating 8–10% of organic acids and dissolving agents. Dissolving agents provide rapid swelling and the ability to rapidly moisten tablets causing quick dissolution.

Solid Dispersion:

It is the dispersion of one or more active ingredients into an inactive matrix, where the active elements can be present in microscopically crystalline, soluble or amorphous states. Good dissolution and bioavailability can be achieved by solid dispersion of pharmaceutically active ingredients. A decrease in particle size often leads to an improvement in the dissolution rate of poorly soluble drugs through an increase in the effective surface area. It is also used in controlled release formulations. A solid dispersion is a physical mixture that is, partially or completely, a molecular level mixture during its formation. Such molecular mixtures increase the surface area of the drug and consequently increase the dissolution rate. In some instances, the drug can be converted to its amorphous state as a result of solid dispersion formation, which would offer a higher dissolution rate due to its higher thermodynamic activity. Solid dispersion can reduce the molecular dynamics of a drug to increase its glass transition temperature and result in improved physical stability of the drug.

- **Methods of preparation:**

Solid dispersion can be prepared by the following methods;

- Melting Method.

- Solvent Evaporation Method.
- Melting Solvent Method.
- Hot Melt Extrusion Technique.
- Dropping Method.
- Spray Drying.
- Supercritical Fluid Technology.

Melting Method: It is used to prepare rapid release solid dispersions. The physical mixture of a drug and a water-soluble carrier is heated until it is melted. The molten mass is cooled again and rapidly freezes on the ice bath with vigorous stirring. The final solid mass is crushed, pulverized and sieved.

Solvent Evaporation Method: This method is used in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. They are prepared by dissolving the physical mixture of two solid components in a solid solvent, followed by evaporation of the solvent.

Melting Solvent Method: In this method, solid fluid is prepared by first dissolving a drug in a suitable liquid solvent and then by directly cooperating the solution in a melt of PEG without removing a liquid. 5–10% of liquid compounds can be incorporated into polymers such as PEG 6000, without significant loss of their solid property.

Hot-melt Extrusion: Hot-melt extrusion (HME) is a process of converting a raw material into a product of uniform size and density that forces it to die under controlled conditions. HMEs use heat to convert raw materials into homogeneously mixed masses, namely, solid dispersion without using organic solvents. The intimately mixed hot mass is ejected through the opening of the die. Extruded hot strands can either be molded or cut into fine unit dosage forms. Alternatively, they can be cooled, shaped and either compacted or compacted into tablets.

Dropping Method: This method is developed to facilitate crystallization of different chemicals. It is a new process for the production of round particles from dispersed molten

solids. It involves dropping a mixture of drug and carrier onto a plate, where it freezes into round particles.

Super Critical Fluid Technology: A supercritical fluid (SCF) there is a substance that exists above its critical point, defined by the temperature and pressure conditions at which the liquid and gaseous states of the substance coexist. When a liquid is heated, its density decreases while the density of vapor continues to increase. At the critical point, the densities of liquid and gas are the same and there is no phase boundary. Above the critical point, which is in the supercritical region, the fluid has the penetrating power of a gas and the solvent strength of the liquid. One application of the SCF process is the rapid expansion of Super Critical Solutions (RESS). During the RESS process, SCF (CO_2) is used as a solvent in which the matrix and the drug are dissolved and sprayed through a nozzle, with low pressure, into an expansion vessel that is exposed to the particles. Adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is said to be solvent free. However, the application of this technique is very limited, as the solubility of most pharmaceutical compounds in CO_2 is very low and decreases with polarity.

Spray Drying:

Spray drying is a process in which drug substances and carrier solutions are evaporated into a chamber as a solution that is maintained under controlled conditions of heat, humidity, and airflow. The dissolution rate of many poorly water-soluble drugs has been enhanced using spray drying. Organic solvents are commonly used during the spray-drying process, as they are easy to evaporate and have good solvent capacity for many poorly water-soluble drugs. The morphology of the solid dispersion and the resulting drug dissolution and stability can be influenced by the process parameters and geometry of the device. For example, varying the concentrations of solutes in the spray in the spray drying process and the droplet size during the spray drying process can control the solid size of the spray. Spray drying techniques have been an important and widely applied technique in the pharmaceutical and biochemical fields. In particular, spray drying can be applied to either heat-resistant and heat sensitive drugs, either to water-soluble and water-insoluble drugs, or to both hydrophilic and hydrophobic polymers.

METHODOLOGY

Table No. 1: Drug/Excipients/Solvents Source

Drug / Excipient /Solvent	Source
Nifedipine	Rydberg Pharmaceuticals Private Limited, Dehradun
Manitol	Evonik Degussa India Private Limited, Mumbai
Sodium starch Glycolate	International Specialty Product, Hong Kong Ltd.
Sodium Starch Glycolate	JRS Pharma, Rosenberg (Germany).
Croscarmellose Sodium	The Anglo French Drug Co. Limited, Bangalore.
Microcrystalline Cellulose	The Anglo French Drug Co. Limited, Bangalore
Mannitol	S.D. Fine Chemicals Limited, Mumbai
Lactose	S.D. Fine Chemicals Limited
Magnesium stearate	S.D. Fine Chemicals Limited
Methanol	S.D. Fine Chemicals Limited
Ethanol	S.D. Fine Chemicals Limited
Petroleum ether	S.D. Fine Chemicals Limited

Table No. 2: LIST OF EQUIPMENTS AND INSTRUMENTS

Equipment/Instruments	Manufacturer
Analytical balance	Shimadzu BL220H, Japan
Rotary tablet press	Rimek RSB-4 minipress, karnavathi, engineering Ahmedabad
USP II dissolution tester	TDT-08L, Electrolab, India
Digital pH meter	Digisun electronics, Hyderabad
Friabilator	Electrolab EF-2, India.
Bulk density apparatus	Campbell electronics, Mumbai.
Tablet hardness tester	Campbell electronics, Mumbai.
Digital vernier caliper	Baker gauzes India ltd.
USP disintegration tester	Electrolab ED-2, India
Thermostatic hot air oven	Serwell instruments, Bangalore

- **PREPARATION OF SOLID DISPERSION:**

The nifedipine - Mannitol solid dispersion was prepared by the solvent evaporation method. In this method, solid dispersions of nifedipine were prepared by the solvent evaporation

method. The physical mixture of nifedipine and other carriers (Mannitol, PVPK30, PEG 4000, PEG6000, PEG8000 and urea) was dissolved in a sufficient amount of methanol in a beaker and the solution was placed overnight in a petri dish for evaporation. The product obtained was scraped and powdered. The percentage yield was found to be 85%.

- **CHARACTERIZATION OF NIFEDIPINE-MANNITOL SOLID DISPERSIONS:**

The formulated drug-Mannitol solid dispersions were characterized by dissolution studies. The in-vitro dissolution study of the prepared solids dispersion was performed using the USP (type-2) mechanism at a speed of 50 rpm. Dissolution studies were performed using 900 mL of phosphate buffer pH 4 as the dissolution medium maintained at a temperature of 37°C ml 5 ± C. At appropriate intervals, 1 mL of the solution was taken and the dissolution medium was replaced with 1 mL of fresh dissolution fluid to maintain a constant volume.

- **FORMULATION OF FDTs CONTAINING NIFEDIPINE-MANNITOL SOLID DISPERSIONS:**

Tablets containing nifedipine-Mannitol solid dispersions were prepared using various superdisintegrants such as crospovidone (CRP) and Croscarmellose sodium (CCS). The tablets were prepared by direct chemical method.

Procedure:

- The tablets were prepared by direct compression method.
- All the ingredients were passed through a screen number 20 prior to mixing.
- Nifedipine-Mannitol solid dispersion, the superdisintegrants and the other excipients were properly mixed for 30 min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate for 5 minutes.
- The blend was compressed into tablets with an average weight of 150 mg using a 6 mm flat punch in a rotary tablet press.

- **PREPARATION OF SOLID DISPERSION:**

The nifedipine- Mannitol solid dispersion was prepared by the solvent evaporation method. In this method, solid dispersions of Nifedipine were prepared by the solvent evaporation

method. The physical mixture of nifedipine and other carriers (Mannitol, PVPK30, PEG 4000, PEG6000, PEG8000 and urea) was dissolved in a sufficient amount of methanol in a beaker and the solution was placed overnight in a Petri dish for evaporation. The product obtained was scraped and powdered. The percentage yield was found to be 85%.

- **Table No. 3(a): Formulation FC, F1-F4**

SAMPLE		FC		F1		F2		F3		F4	
S.No.	**Ingredients**	**Q**	**P**	**Q**	**P**	**Q**	**P**	**Q**	**P**	**Q**	**P**
1.	Nifedipine Manitol Solid Dispersion	50	33	50	33	50	33	50	33	50	33
2.	Manitol	14	9	10	7	10	7	10	7	10	7
3.	Lactose	77	51	80	53	79	53	78	52	77	51
4.	Magnesium stearate	2	1	2	1	2	1	2	1	2	1
5.	Talc	3	2	3	2	3	2	3	2	3	2
6.	Sucrose	3	2	3	2	3	2	3	2	3	2
7.	Citric acid	1	1	1	1	1	1	1	1	1	1
8.	Croscarmellose Sodium	0	0	1	1	2	1	3	2	4	3
9.	Sodium Starch	0	0	0	0	0	0	0	0	0	0

Q: Quantity per tablet (mg) P: Percentage per tablet

Table 3(b): Formulation F5-F8

SAMPLE		F5		F6		F7		F8	
S. No.	**Ingredients**	**Q**	**P**	**Q**	**P**	**Q**	**P**	**Q**	**P**
1.	Nifedipine-Manitol Solid Dispersion	50	33	50	33	50	33	50	33
2.	Manitol	10	7	10	7	10	7	10	7
3.	Lactose	80	53	79	53	78	52	77	51
4.	Magnesium stearate	2	1	2	1	2	1	2	1
5.	Talc	3	2	3	2	3	2	3	2
6.	Sucrose	3	2	3	2	3	2	3	2
7.	Citric acid	1	1	1	1	1	1	1	1
8.	Sodium Starch Glycolate	1	1	2	1	3	2	4	3
9.	Croscarmellose Sodium	0	0	0	0	0	0	0	0

Q: Quantity per tablet (mg) P: Percentage per tablet

Table 3(c): Formulation F9-F12

SAMPLE		F9		F10		F11		F12	
S.No.	**Ingredients**	**Q**	**P**	**Q**	**P**	**Q**	**P**	**Q**	**P**
1.	Nifedipine-Manitol Solid Dispersion	50	33	50	33	50	33	50	33
2.	Manitol	10	7	10	7	10	7	10	7
3.	Lactose	77	51	77	51	77	51	77	51
4.	Magnesium stearate	2	1	2	1	2	1	2	1
5.	Talc	3	2	3	2	3	2	3	2
6.	Sucrose	3	2	3	2	3	2	3	2
7.	Citric acid	1	1	1	1	1	1	1	1
8.	Croscarmellose Sodium	3	2	2	1	1	1	3	2
9.	Sodium Starch Glycolate	1	1	2	1	3	2	2	1

Q: Quantity per tablet(mg) P: Percentage per tablet

Table 3(d): Formulation F13-F16

SAMPLE		F9		F10		F11		F12	
S.No.	**Ingredients**	**Q**	**P**	**Q**	**P**	**Q**	**P**	**Q**	**P**
1.	Nifedipine-Manitol Solid Dispersion	50	33	50	33	50	33	50	33
2.	Manitol	10	7	10	7	10	7	10	7
3.	Lactose	77	51	77	51	77	51	77	51
4.	Magnesium stearate	2	1	2	1	2	1	2	1
5.	Talc	3	2	3	2	3	2	3	2
6.	Sucrose	3	2	3	2	3	2	3	2
7.	Citric acid	1	1	1	1	1	1	1	1
8.	Sodium Starch Glycolate	1	1	3	2	3	2	2	1

F. EVALUATION:

POWDER BLENDPROPERTIES:

- Determination of density.
- Percentage compressibility or Carr's index.
- Hausner ratio.
- Angle of repose.

- **Determination of Density:**

A simple test was used to evaluate the flow capacity of the powder by comparing the flow density (λBmin) of the powder and the density (λBmax) of the tape and the rate at which it was packed down. Tape density was determined by taking 20 g of the powder mixture in a cylinder measuring 20 ml 50 ml and tapping a constant volume in a bulk density apparatus.

- **Percentage compressibility or Carr's index:**

Based on the poured density and tapped density, the % compressibility of the powder blend was computed using the Carr's index:

$$\text{Carr's index (\%)} = (TD - BD)/TD \times 100$$

Where, TD = Tapped density

BD = Bulk density

Table No. 4: Carr's Index as an indication of powder flow

CARR'S INDEX (%)	TYPE OF FLOW
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

- **Hausner Ratio:**

Table No. 5: Hausner ratio as an indication of powder flow

HAUSNER RATIO	TYPE OF FLOW
Less than1.25	Good flow
Greater than1.25	Poor flow
Between1.25-1.5	Addition of glidant normally improves the flow

- **Angle of Repose:**

The angle of the repose of the powder mixture was determined by the height and cone method.

A funnel was fixed to the desired height and filled with a powder mixture. They were allowed to flow downward onto a graph paper fixed on a horizontal surface. The angle of repose was calculated using the formula:

$$Tan\theta = 2h / D$$

Where h and d are height and diameter of the pile respectively.

Table No. 6: Angle of repose as an indication of powder flow properties

ANGLE OF REPOSE (DEGREES)	TYPE OF FLOW
<20	Excellent
20-30	Good
30-34	Passable*
>40	Very poor

*May be improved glidant.

- **TABLET PROPERTIES:**

The finished tablets were evaluated,

- **Thickness:** Six tablets were randomly selected and the thickness of each was measured by a digital Vernier caliper. Mean and standard deviation calculated and reported.

- **Hardness:** The hardness of the ten tablets was measured using the Monsanto Hardness Tester. Mean and standard deviations were calculated and reported. It is expressed in kg / cm^2.

- **Friability:** Stability of the tablets was determined using a Roche Friabilator. The tablets were initially weighed and red transferred to the Friabilator. The Friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again after 4 minutes. The % friability was then calculated using the formula:

% Friability = (W1-W2) x 100

- **Weight Variation:**

Twenty tablets were weighed individually and the average weight was calculated. Individual weights were compared to mean weights. If the tablet does not exceed two percent, then the tablets pass the test and if the belt does not exceed twice the percentage limit. The weight variation to clearance for uncoated tablets is as follows:

Table No. 7: Values of weight variation and comments

Average Weight of Tablets(mg)	Maximum Percentage Difference Allowed
130 or less	10
130-324	7.5
More than324	5

- **Disintegration Test:** The dissolution test was performed using the USP dissolution test device type-II. Six tablets were separately placed in each tube of the dissolution test device and a disk was placed on each tablet. The phosphate buffer pH 7.4 was used as the medium formed at 37^0C + 0.5^0C and the time taken to completely decompose each tablet was recorded.

- **Wetting Time:** The wetting time of the dosage form is related to the contact angle. The wetting time of FDT is another important parameter that needs to be evaluated to give an insight into the dissolution properties of the tablet. Shorter wetting time means early dissolution of the tablet. The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a diameter of 10 cm. Ten milliliters of water-soluble dye solution were added to Petri dish. A tablet was carefully placed on the tissue paper surface.

- **Drug Content Uniformity:** Ten tablets were randomly selected and allowed to equilibrate with Phosphate buffer pH 7.4 (without enzyme) overnight and the solution was filtered (0.22, Millipore) after24 hours. Suitable dilutions were made with the same to get the concentration in Beer's range. Absorbance of the solution was noted at 314 nm using Phosphate buffer pH 7.4 as blank and drug content per tablet was calculated.

- **In-vitro Dissolution Study:** Dissolution study was carried out using USP XXII dissolution test apparatus type II. The dissolution medium used was 900 ml of Phosphate buffer pH 7.4(without enzyme) which was maintained at 37^0C. The paddle speed was kept at 50 rpm throughout the study. Two ml of samples was withdrawn at every 10 minutes interval and diluted to 10 ml then 1ml of fresh dissolution media maintained at the same temperature was replaced. The samples were analyzed spectrophotometrically at 237.5 nm using Phosphate buffer pH 7.4(without enzyme) as blank. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals. For finding out the mechanism of drug release from FDTs, the dissolution data obtained from the experiments were treated with the different release kinetic and mechanism equations.

4. RESULTS

Table No. 8: Solubility study of nifedipine in various solvents

S. No/	Solvent	Solubility(mg/ml)
1	Water	0.001
2	Acetone	302.7
3	Methylene Chloride	119.3
4	Chloroform	81.6
5	Methanol	32
6	Ethanol	13.81
7	Phosphate Buffer pH7.4	0.025
8	Phosphate Buffer pH8	0.012

Solubility Studies of Nifedipine with various carriers

Table No. 9: Data for solubility studies in Phosphate Buffer pH 7.4

Concentration (Percentage)	Solubility of Mannitol	Solubility of PVP K30 (µg/ml)	Solubility of PEG 4000 (µg/ml)	Solubility of PEG 6000 (µg/ml)	Solubility of PEG 8000 (µg/ml)	Solubility of Urea (µg/ml)
2	8.806	4.233	2.525	2.273	4.309	10.138
4	11.05	6.193	3.844	3.781	6.708	10.40
6	11.8	9.829	4.912	5.804	8.881	10.904
8	12.374	10.113	6.118	6.922	10.314	11.645
10	12.525	12.198	7.37	9.082	12.939	12.21

Concentration (%w/v)

Table No. 10: *In-vitro* dissolution study data for Solid Dispersion of PEG8000

Time (min)	% Cumulative Release			
Sample	Drug to Carrier ratio			
00	01:01	01:02	01:03	01:04
10	1.35	2.15	3.23	4.32
20	5.93	6.02	9.65	12.99
30	9.07	10.89	14.14	16.02
40	13.03	18.82	21.38	27.98
50	14.31	21.03	28.37	31.31

Table No. 11: *In-vitro* dissolution study data for Solid Dispersion of Mannitol

Time (min)	% Cumulative Release			
	Drug to Carrier ratio			
00	01:01	01:02	01:03	01:04
10	3.01	4.05	5.28	6.65
20	7.67	8.54	9.83	13.05
30	11.13	13.89	15.24	17.73
40	14.31	22.14	23.32	28.94
50	16.12	22.91	30.41	37.47

Table No. 12: *In-vitro* dissolution study data for Solid Dispersion of Urea

Time (min)	% Cumulative Release			
	Drug to Carrier ratio			
00	01:01	01:02	01:03	01:04
10	2.21	3.15	5.24	5.01
20	6.23	9.45	9.73	12.01
30	10.53	12.67	14.5	17.12
40	13.99	19.41	22.68	27.04
50	15.66	23.01	30.01	36.99

Table No. 13: Percentage Release at 50 min by various carriers

Polymer	01:01	01:02	01:03	01:04
PEG8000	14.31	21.03	28.37	31.31
Mannitol	16.12	22.91	30.41	37.47
Urea	15.66	23.01	30.01	36.99

- **PRECOMPRESSION EVALUATION OF THE POWDER BLEND**

Table No. 14: Result of flow properties of formulations (FC,F1- F16).

Formulation	Poured Density* (gm/ml3)	Tapped density*(gm)	Carr's index	Hausner ratio (%)	Angle of repose* (degree)
FC	0.539	0.668	19.3	1.24	$25^{o}16'$
F1	0.521	0.645	19.22	1.24	$22^{o}65'$
F2	0.537	0.66	18.63	1.23	$23^{o}73'$
F3	0.518	0.645	19.69	1.24	$28^{o}20'$
F4	0.535	0.66	18.94	1.23	$28^{o}39'$
F5	0.532	0.663	19.76	1.25	$27^{o}31'$
F6	0.53	0.653	18.84	1.23	$26^{o}28'$
F7	0.542	0.675	19.7	1.24	$29^{o}66'$
F8	0.538	0.658	18.24	1.22	$27^{o}48'$
F9	0.585	0.675	13.33	1.22	$23^{o}54'$
F10	0.537	0.662	18.88	1.23	$24^{o}70'$
F11	0.541	0.668	19.01	1.24	$26^{o}59'$
F12	0.539	0.663	18.7	1.23	$24^{o}89'$
F13	0.525	0.651	19.35	1.24	$21^{o}40'$
F14	0.523	0.652	19.78	1.25	$24^{o}12'$
F15	0.522	0.655	20.3	1.25	$25^{o}35'$
F16	0.518	0.641	19.19	1.24	$27^{o}08'$

* The values represents mean, n =3

D. TABLET PROPERTIES:

Table No. 15: Results of tablet properties of formulations (FC, F1-F16)

Formulation	Wt. variation	Wetting time*	Drug content uniformity
FC	0.539	0.668	19.3
F1	0.521	0.645	19.22
F2	0.537	0.66	18.63
F3	0.518	0.645	19.69
F4	0.535	0.66	18.94
F5	0.532	0.663	19.76
F6	0.53	0.653	18.84
F7	0.542	0.675	19.7
F8	0.538	0.658	18.24
F9	0.585	0.675	13.33
F10	0.537	0.662	18.88
F11	0.541	0.668	19.01
F12	0.539	0.663	18.7
F13	0.525	0.651	19.35
F14	0.523	0.652	19.78
F15	0.522	0.655	20.3
F16	0.518	0.641	19.19

* The values represents mean± SD, n =3

Table No. 16: Results of Post Compression Evaluation of formulations (FC-F16)

Formulation	Thickness[A] (mm)	Hardness[B] (Kg/cm2)	Friability (Percentage)	Disintegration time[C] (sec)
FC	2.10±0.07	3.17±0.30	0.44	100
F1	2.10±0.04	3.36±0.12	0.54	70
F2	2.11±0.07	3.23±0.27	0.73	62
F3	2.11±0.06	3.26±0.19	0.66	59
F4	2.11±0.08	3.45±0.22	0.51	57
F5	2.12±0.04	3.13±0.29	0.83	65
F6	2.12±0.05	3.10±0.23	0.48	61
F7	2.11±0.03	3.58±0.25	0.72	57
F8	2.12±0.04	3.11±0.26	0.62	56
F9	2.11±0.05	3.12±0.34	0.63	54
F10	2.11±0.07	3.53±0.25	0.75	53
F11	2.10±0.03	3.14±0.20	0.32	50
F12	2.10±0.06	3.23±0.15	0.42	57
F13	2.11±0.05	3.21±0.18	0.83	52
F14	2.12±0.01	4.00±0.13	0.6	51
F15	2.12±0.02	3.14±0.17	0.4	49
F16	2.11±0.06	3.67±0.14	0.5	55

A-Average of 6 readings SD, B- Average of 10 readings SD, C- Average of6 readings SD

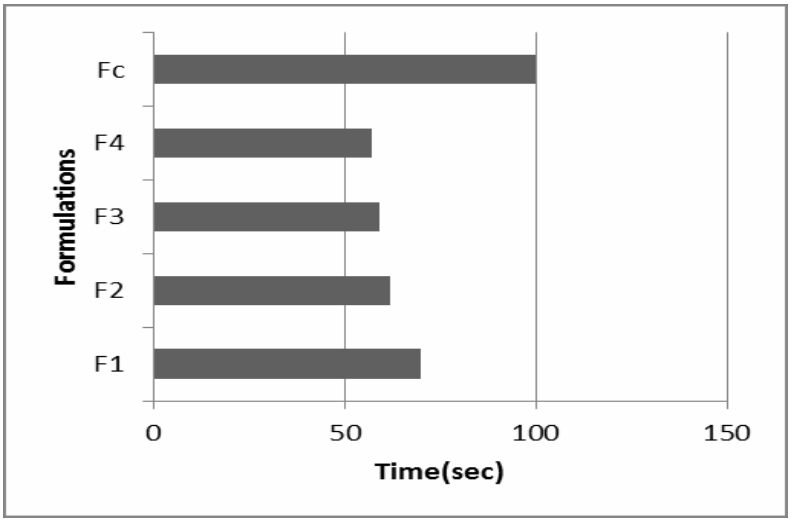

Figure No. 1: Disintegration Time for Formulation Fc, F1-F4

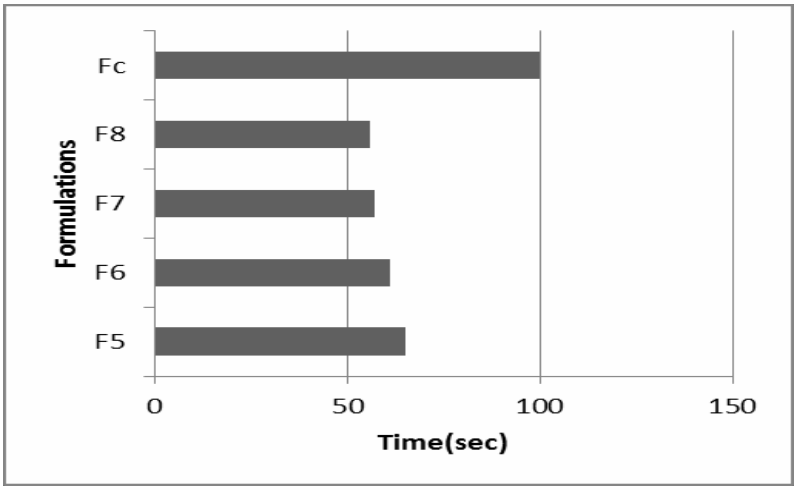

Figure No. 2: Disintegration Time for Formulation Fc, F5-F9

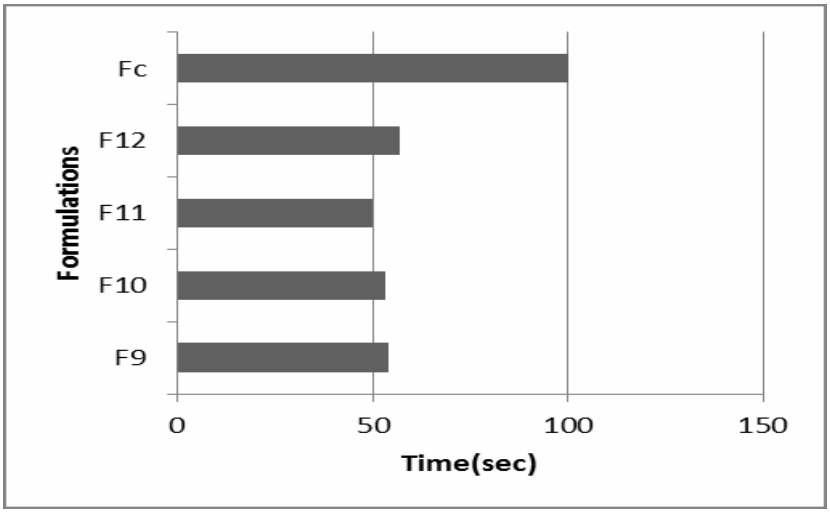

Figure No. 3: Disintegration Time for Formulation Fc,F9-F12

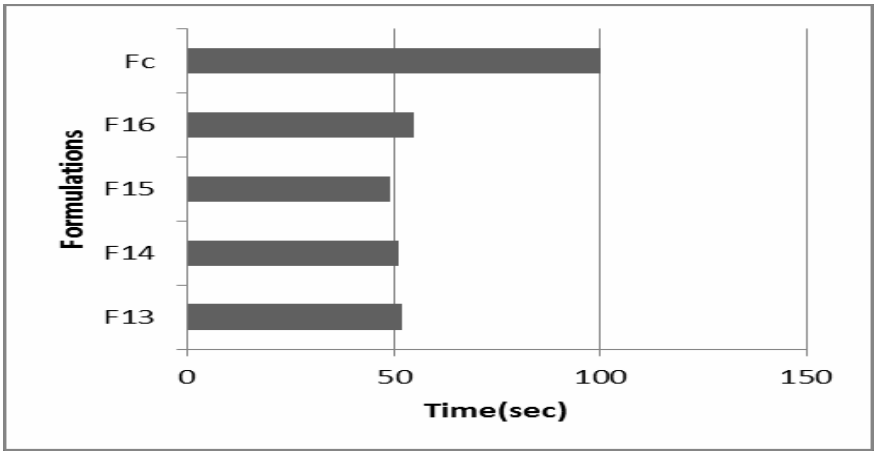

Figure No. 4: Disintegration Time for Formulation Fc, F9-F12

Table No. 17: *In-vitro* dissolution profile of formulations FC, F1-F16

	%Cumulative Release																
Time(min)	**FC**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
10	4.32	26.2	27.8	29	31	28	28.9	30	31	29.9	31.3	32.9	31	30	32.8	31.1	30.7
20	13	37	38	38.7	41	38.1	39.2	40.1	41.2	40.9	42	44	39.9	41.5	43.2	42.8	41.1
30	16	47	47.9	49	51	48.2	49.1	50	50.9	51	52.2	55	51	50	53.1	52	51.3
40	28	57.2	58	58.9	61	58	58.8	60.2	61.4	61	63	64	60	60	63	61.9	61
50	38.8	67.3	67.9	69.5	71.3	68.3	69.2	70.1	71.6	71.3	72.6	73.3	70	70	73	74	71.5

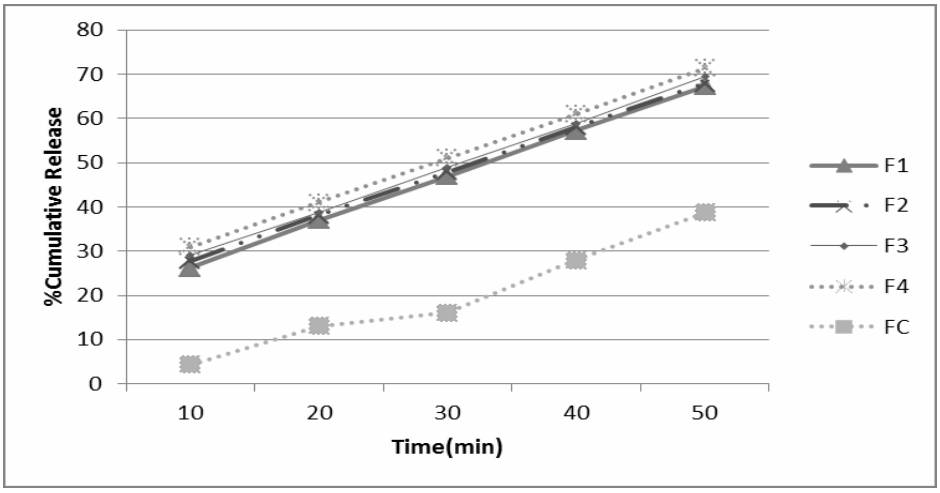

Figure No. 5: *In-vitro* dissolution profile of formulations FC, F1-F4

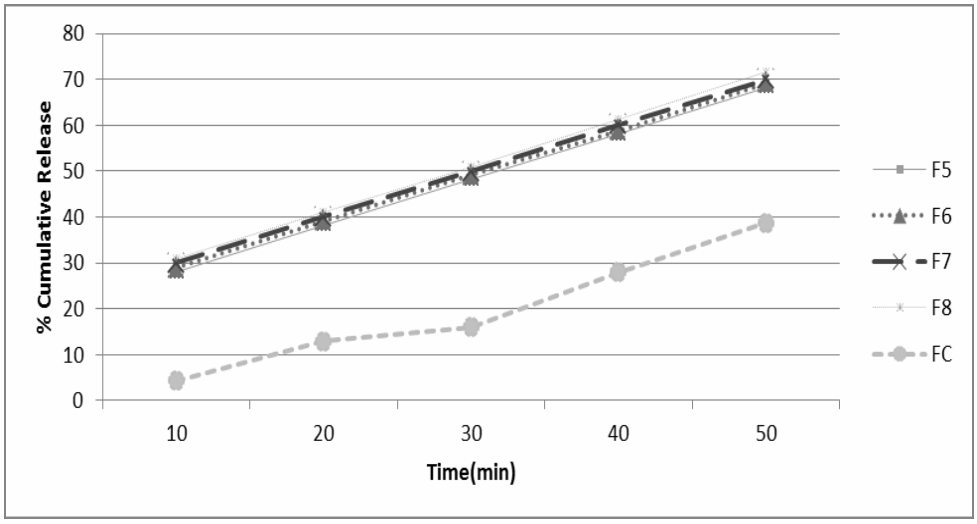

Figure No. 6: *In-vitro* dissolution profile of formulationsF5-F8

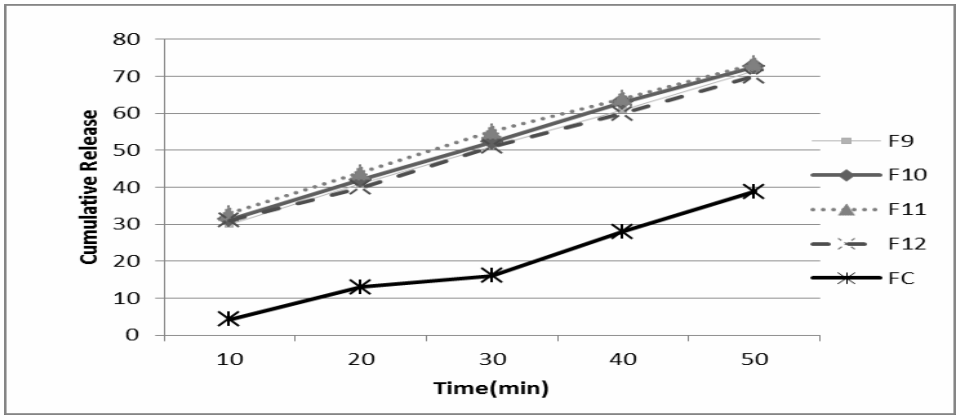

Figure No. 7: *In-vitro* dissolution profile of formulations F9-F12

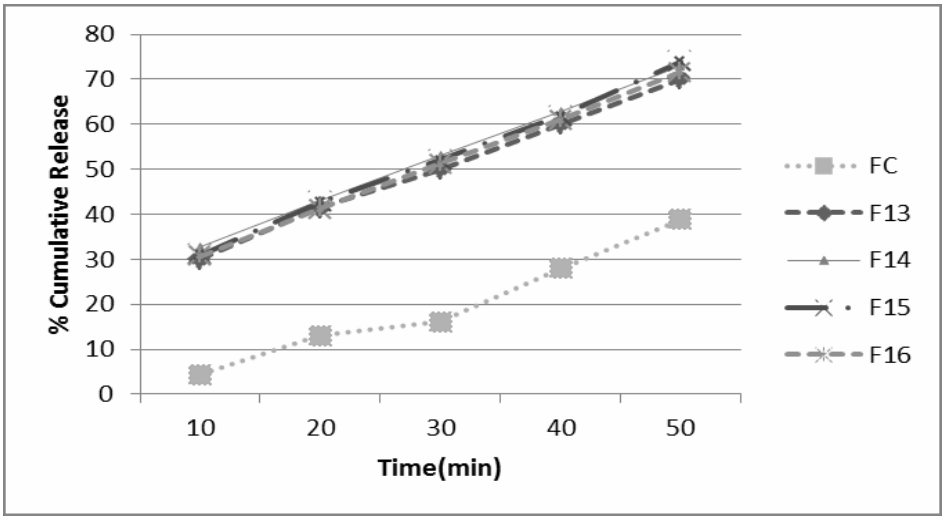

Figure No. 8: *In-vitro* dissolution profile of formulationsF13-F16

DISCUSSION

In the present work, an attempt has been made to increase the solubility of nifedipine by preparation of solid dispersions and to prepare fast dissolution tablets of nifedipine using various techniques. The drug – excipient interaction study was then performed using the super saturation method to determine the solubility of nifedipine in solutions of different solvents and different carriers.

Thus according to the data in Table 9, nifedipine was found to be soluble in acetone, methylene chloride, chloroform, methanol, ethanol, and ethyl alcohol, but was practically insoluble in water. The solubility in phosphate buffers of pH 7.4 and 8 was found to be 0.025 and 0.012, respectively, which indicated very poor solubility. Thus an attempt was made to increase the solubility of nifedipine in a phosphate buffer of pH 7.4 i.e. a buffer simulating saliva in the mouth by forming a solid dispersion.

The solubility of nifedipine was studied using the super saturation method to determine the solubility of nifedipine in solutions of different carriers. The carrier for the preparation of solid dispersions was selected based on solubility studies in phosphate buffer pH 7.4. The results are shown in Table 10 and shown in Figure. From the data in Table 10 it was observed that the solubility of nifedipine increased, as did the concentrations of Mannitol, urea, PVPK30 and PEG 8000. Solubility was also increased with PEG 4000 and PEG 6000, but to a lesser extent.

CONCLUSION

Solid dispersion that lead to the greatest increase in solubility (nifedipine: mannitol-1: 4) was used in the preparation of rapidly dissolving tablets. The tablets were prepared by the direct compression method using two different superdisintegrants. The desired results (49 seconds) were obtained with formulations containing nifedipine - Mannitol solid dispersion (1: 4), prepared by the solvent evaporation method and containing a co-processed mixture of Croscarmellose sodium and sodium starch Glycolate. Thus it can be concluded that FDT with Nifedipine-Mannitol solid dispersion with reduced dissolution time can be prepared by direct compression method using a co-processed mixture of Croscarmellose sodium and sodium starch Glycolate with 1% and 2% are carried out in the ratio of superdisintegrants respectively.

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