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Original Research Article

Develop and evaluate a smart film Tablet from tissue paper that is capable enough to increase the dissolution profile of BCS class-II drug Cilnidipine

*Makwana Rajeshree

Sardar Patel College of Pharmacy, Bakrol, Gujarat

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***Corresponding author:** Makwana Rajeshree
Sardar Patel College of Pharmacy, Bakrol, Gujarat

Abstract

Newly developed API cilnidipine from BCS class-II which has high permeability and low solubility hence increased solubility by smart film tablet. The main objective of the work was to improve the drug dissolution rate using smart film technology. The smart film technique is a novel approach to overcome poor solubility. The technique uses commercial paper in which cilnidipine drug can be loaded onto the paper, it can be a creative and innovative way to increase the dissolution rate of cilnidipine drug. The tablets appear shiny and with a smooth surface. The pharmaceutical quality was acceptable, i.e. all tablets fulfilled the requirements for tablets. Drug-loaded tablets were produced by compression of drug-loaded paper. Drug loading did not alter the pharmaceutical quality. However, the uncoated tablets possessed an extremely fast disintegration, i.e. intense swelling upon contact with water, which might hamper the swallowing after oral administration. In fact, tablets made from paper are a novel and promising strategy for improved oral drug delivery. They can be easily produced without any further excipients and possess pharmaceutical quantity. These are the different papers like Kitchen roll, disposable handkerchief, coffee filter paper, and envelope paper which are used in preparation of smart film tablet. Tablets were subjected to characterization such as thickness, hardness, friability, weight uniformity, drug content, disintegration time, and In-vitro drug release. The In vitro drug release in optimized formulation T1 was found to be 99.21 % in 5 min and disintegration time was found to be 14 sec.In vitro dissolution results are subjected to statistical analysis and found that the formulation (T1) has shown an increased dissolution rate (99.21% at 5 min), compared to the marketed formulation (36.71%in 5min).

Keywords: *Cilnidipine, Smart-film tablet, cellulose based paper, hypertension, oral drug delivery.*

INTRODUCTION:

Hypertension

It is a medical condition in which the blood pressure (arterial blood pressure) is increased normally blood pressure is 120/80 mmHg.Hypertension, also known as high blood pressure, is a common condition where the force of blood against the artery walls is consistently too high. It's often called the "silent killer" because it can lead to serious health issues like heart disease, stroke, and kidney problems if left untreated. Management typically involves lifestyle changes and, in some cases, medication. Regular check-ups are essential for monitoring blood pressure levels. Hypertension is one of the most important risk factors for cardiovascular diseases, including ischemic and hemorrhagic stroke, dementia, ischemic heart disease, heart failure, vision loss, and kidney failure. Hypertension is a multifactorial and multifaceted disease in which elevated blood pressure is only one sign of multiple underlying physiological abnormalities. Hypertension or high blood pressure is a leading cause of death. The condition is often called a silent killer" because its symptoms can go undetected until damage to the body has occurred. Because of this, it is one of the most significantly under-diagnosed and under-treated medical conditions all over the world. High blood pressure is usually a lifelong condition. High blood pressure can occur at any age but is particularly prevalent in people with a family history of high blood pressure, people who are overweight or obese, people with diabetes, and heavy drinkers.

1.2 Symptoms:

- Headache
- Heaviness of chest
- Shortness of breath
- Pain in legs
- Urination in Night
- Nausea
- Muscle weakness

1.3 Types of Hypertensions

Hypertension can be classified into two main types:
Primary (essential) hypertension: This is the most common type and develops gradually over time with no identifiable cause. It's often related to lifestyle factors such as diet, exercise, and stress.
Secondary hypertension: This type is caused by an underlying condition, such as kidney disease, hormonal disorders, or certain medications. Treating the underlying cause can often help manage secondary hypertension.

1.4 Causes:

Lifestyle factors: Poor diet high in sodium, low in potassium, lack of physical activity, obesity, excessive alcohol consumption, and smoking can all contribute to hypertension.

Genetics: Family history plays a significant role in hypertension risk. If your parents or close relatives have hypertension, you may be at higher risk.

Age: As people get older, the risk of developing hypertension increases. This is partly due to the natural aging process and partly due to lifestyle factors that accumulate over time.

Medical conditions: Certain medical conditions can increase the risk of hypertension, including kidney disease, diabetes, sleep apnea, and hormone disorders (such as thyroid disorders or adrenal gland tumors).

Medications: Some medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), decongestants, birth control pills, and certain antidepressants, can elevate blood pressure.

Stress: Chronic stress or frequent exposure to stressful situations can lead to hypertension by causing the body to release stress hormones that constrict blood vessels and raise blood pressure.

Other factors: Other factors that can contribute to hypertension include race (African-Americans are at higher risk), socioeconomic status, and environmental factors like pollution or noise levels.

1.5 Complications:

Cardiovascular diseases: High blood pressure increases the risk of heart attack, stroke, heart failure, and other cardiovascular diseases by damaging the arteries and making the heart work harder to pump blood.
Kidney damage: Hypertension can cause kidney damage over time by impairing the blood vessels in the kidneys, leading to reduced kidney function or even kidney failure.
Eye damage: High blood pressure can damage the blood vessels in the eyes, leading to vision problems or even blindness over time. This condition is known as hypertensive retinopathy.
Aneurysms: Persistent high blood pressure can weaken the walls of arteries, potentially leading to the formation of aneurysms (bulges) in blood vessels. Aneurysms can rupture, causing life-threatening internal bleeding.
Peripheral arterial disease (PAD): Hypertension can lead to the narrowing and hardening of arteries in the limbs, reducing blood flow to the legs and arms. This can cause pain, numbness, or even tissue death (gangrene).
Cognitive decline: Chronic hypertension has been linked to cognitive decline and an increased risk of dementia, including Alzheimer's disease.
Sexual dysfunction: Hypertension can contribute to erectile dysfunction in men and decreased libido or arousal difficulties in both men and women.

1.6 Risk factors:

Age: The risk of hypertension increases with age. As people get older, their blood vessels lose flexibility, making them more prone to high blood pressure.

Family history: Having close relatives with hypertension increases your risk of developing it.

Race: Certain ethnic groups, such as African Americans, are at higher risk of hypertension.

Obesity and overweight: Being overweight or obese increases the risk of hypertension because it puts extra strain on the heart and increases blood volume.

Unhealthy diet: Consuming too much sodium (salt) and too little potassium in your diet, as well as excessive alcohol intake, can contribute to hypertension.

Physical inactivity: Lack of regular physical activity can lead to weight gain and increase the risk of hypertension.

Smoking: Tobacco smoke damages blood vessels and increases the risk of hypertension and other cardiovascular diseases.

Stress: Chronic stress can lead to elevated blood pressure, though the exact mechanisms are not fully understood.

Chronic conditions: Conditions such as diabetes, kidney disease, and sleep apnea increase the risk of hypertension.

High cholesterol levels: Elevated levels of cholesterol and triglycerides in the blood can contribute to the development of hypertension.

Medications: Some medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), decongestants, and oral contraceptives, can increase blood pressure.

Managing these risk factors through lifestyle changes, such as adopting a healthy diet, regular exercise, maintaining a healthy weight, quitting smoking, managing stress, and following medical advice for underlying conditions, can help prevent or control hypertension. Regular blood pressure monitoring and medical check-ups are also important for early detection and management.

1.7 Pathophysiology

Renin-angiotensin-aldosterone system (RAAS) activation: When blood pressure decreases or there's a decrease in blood flow to the kidneys, the RAAS is activated. Renin, released by the kidneys, converts angiotensinogen into angiotensin I, which is then converted into angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone, which increases sodium and water retention, leading to elevated blood pressure.

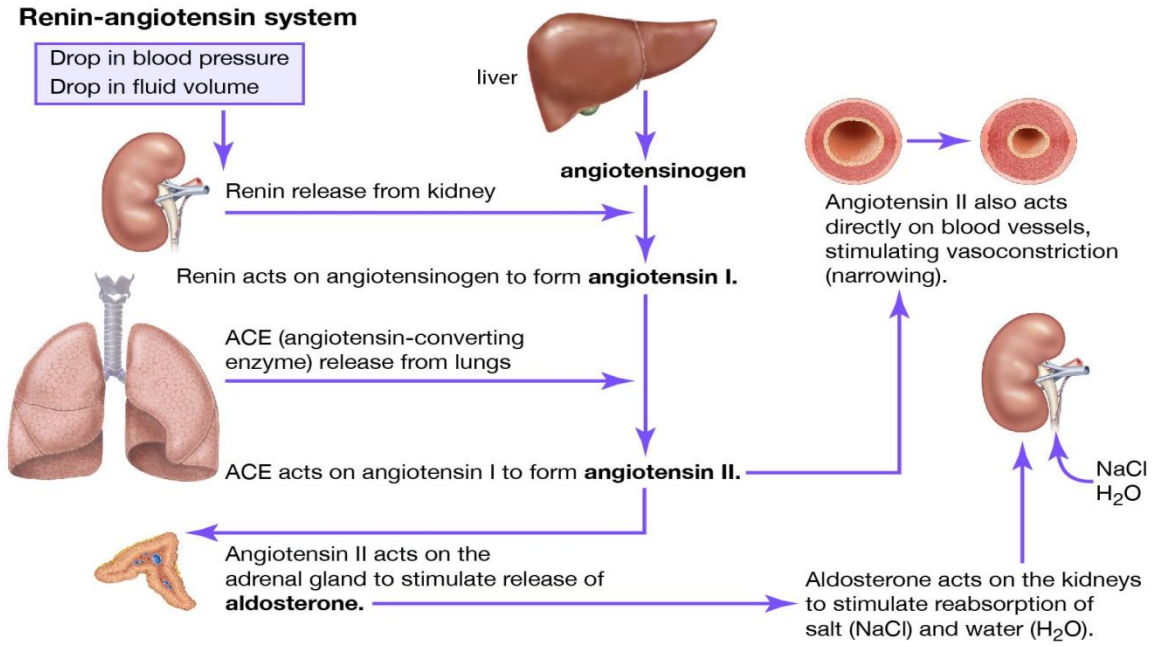


Figure1.1. Pathophysiology of Hypertensions disease.

1.8 Diagnosis

- Sphygmonometer
- ECG
- Eco-cardiogram
- Blood test
- Electrolyte level

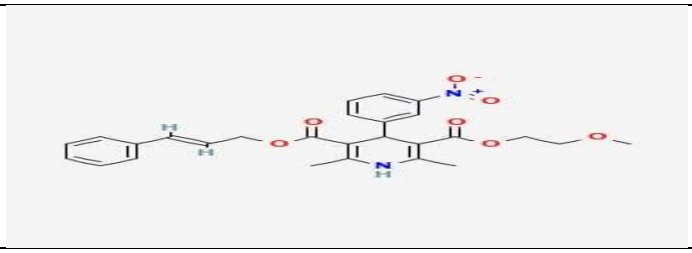
1.9 Treatment

- Non-pharmacological management
- Weight Loss
- Stop Smoking
- Decreases Sodium channel in diet

1.10 Classification of Anti-Hypertensive Drug

1) Diuretics: - furosemide, Amiloride, Hydrochlorothiazide.
2) Beta-Alpha Adrenergic Blockers: - labetalol, carvedilol
3) ACE inhibitors: - captopril, Ramipril, Lisinopril
4) Antagonist Receptor blockers: - losartan, telmisartan, valsartan
5) Calcium channel Blockers: - verapamil, cilnidipine, amlodipine, felodipine
6) Beta blockers: - metoprolol, timolol, satalol
7) Alpha blockers: - terazosin, doxazosin, prazosin
8) Centrally acting sympatholytic: - clonidine, methyldopa
9) Vasodilators: - Minoxide, Diazoxide, nitric oxide

1.11 Drug Profile

1.	**Cilnidipine**	Cilnidipine (CIL) 1,4- Dihydro- 2,6- dimethyl- 4-(3-nitrophenyl)-3,5-pyridinecarboxylic acid 2- methoxyethyl(2E)-3-phenyl-propenyl ester is a novel and unique dihydropyridine calcium channel blocker that possesses a slow-onset, long-lasting vasodilating effect.
2.	**Structure**	
3.	**Molecular formula**	C27H28N2O7
4.	**IUPAC**	Cilnidipine (CIL) 1,4- Dihydro- 2,6- dimethyl- 4-(3-nitrophenyl)-3,5-pyridinecarboxylic acid 2- methoxyethyl(2E)-3-phenyl-propenyl ester
5.	**Category**	Calcium channel blockers
6.	**Characteristics**	Yellow crystalline solid
7.	**Solubility**	Soluble in DMSO (> 25 mg/ml), ethanol (20 mg/ml), water (≤ 2 mg/ml), and methanol.
8.	**BCS class**	Class II
9.	**Molecular weight**	492.52 gm/mole
10.	**Trade name**	Cilcar, Cinod, Cilny
11.	**Mechanism of action**	Cilnidipine is a dual blocker of L-type voltage-gated calcium channels in vascular smooth muscle and N-type calcium channels in sympathetic nerve terminals that supply blood vessels. The inhibition of N-type calcium channels may provide a new strategy for the treatment of cardiovascular diseases. L-type calcium channels are the main targets of the calcium channel blockers. N-type calcium is distributed along the nerve and in the brain, cilnidipine is anticipated to exert specific action on nerve activity, such as inhibition of the sympathetic nervous system. It inhibits the calcium influx in both in vessel & in the nerve. So causes the Vasodilation & inhibits the release of nor

		epinephrine, which causes the Vasodilation and decreases the heart rate & also decreases cardiac contraction in heart. So, used in treatment of hypertension
12.	**Dose**	Adult: 5-10 mg once daily, increase to 20 mg once daily if necessary.
13.	**Pharmacokinetics**	
a)	**Absorption**	Orally absorbed
b)	**Metabolism**	Hepatic. Metabolised extensively (90%) to inactive metabolites via the cytrochrome P450 3a4 iso enzyme.
c)	**Excretion**	Urine
d)	**Peak Plasma Concentration**	6-12 hour following oral administration. Bioavailability is 64-90%.
e)	**Bioavailability**	13%
f)	**Log p value**	4.7
g)	**Shelf life**	24 months.
h)	**Storage**	Store protected from light and moisture at a temperature not exceeding 30-degree celcius.

1.12 Drug Delivery System

A Drug delivery system is defined as a component or a tool that permits the introduction of a healing substance within the body and improves its efficacy and safety by means of controlling the fee, time, and place of release of medicine inside the body. This process consists of the administration of the therapeutic product, the discharge of the active elements via the product. and the subsequent delivery of the lively components across the organic membranes to the site of action. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Gene therapy can fit in the basic and broad definition of a drug delivery system. Gene vectors may need to be introduced into the human body by novel delivery methods. However, gene therapy has its own special regulatory control. Drug delivery system is an interface between the patient and the drug. Delivery of proteins and peptide provides unique challenges. Nanoparticles are important in refining drug shipping: they may be prescription drugs in addition to diagnostics. Refinements in drug transport will facilitate the development of personalize medication, which includes pharmacogenomics, pharmacogenetics, and pharmacoproteomic. A classification of various anatomical routes for systemic drug delivery: Gastrointestinal system, Oral, Rectal, Parenteral, Subcutaneous injection, Intramuscular injection, Intravenous injection, Intra-arterial injection, Transmucosal: Buccal and through mucosa lining the rest of gastrointestinal tract, Trans-nasal, Pulmonary: drug delivery by inhalation, Trans-dermal drug delivery, Intra-osseous infusion.

Experimental:

1. Identification of Drug

1) FI-IR spectroscopy:

FT-IR of drug carryout by Perkin-Elmer 1600 FTIR spectrometer. The FT-IR spectrum of the drug, a pellet of the drug and KBr was prepared using hydraulic pellet press at a pressure of 7-10 tones. FT-IR was Scanned from 400-4000 cm'.The major peaks obtained in the FT-IR spectra of Cilnidipine were found to be correlating with the functional groups present in the structure of the drug.

2) Melting point determination:

The melting point of cilnidipine was determined by Capillary Fusion Method using Digital melting point apparatus. Obtained melting point was compared with standard drugs' melting point.

2. Spectrophotometric estimation of Cilnidipine:

- **Preparation of standard stock solution in methanol**
  Cilnidipine standard stock solution was prepared by the dissolution 100 mg of the standard drug in 100 ml of Methanol and then making up to the mark in a 100 ml standard flask with the same solvent. 1 ml of this solution was transferred to another 10ml volumetric flask and made up to 10 ml with diluent to obtain a 100µg/ml concentration. From this standard stock solution, several concentrations (2-12 µg/ml) of solution were prepared.
- **Determination of λmax.**
  The standard stock solution was diluted in methanol to obtain 6 µg/ml. This solution was measured in the Ultra-Violet region from 200 - 400 nm. The max was obtained as 240 nm. The linear curve was obtained with a graph plotting the absorbance against the concentration.

- **Preparation of Calibration curve in Methanol**
  Aliquot of standard stalk solution 1ml was further dilute up to 10ml with methanol so get 100 µg/ml solution. Solution of different concentration 2,4,6,8,10 µg/ml were prepared using100µg/ml solution. Absorbance of the solution was measured at 240nm.

3. Preparation of smart-film tablet made from paper

For the production of Smart Films pieces of paper were cut out. Loading was performed by applying 1ml of methanol solution in the center of the paper basis with a pipette, which resulted in wetting the whole paper. This led, after drying, to a loading of 1mg drug per cm² paper basis. The drying was performed in a fume hood for approximately an hour at ambient temperature. For each loading Smart Films were prepared. The Smart Films, these were compressed into tablets. This was done by manually filling the powders into the cavity of a tablet press and by manual compression without any further excipients. In addition, tablets were also obtained from the Smart Films. These tablets were obtained by cutting the smart Films into small pieces. Subsequent filling and compression were then done as described above with compression force not exceeding 30 kN.

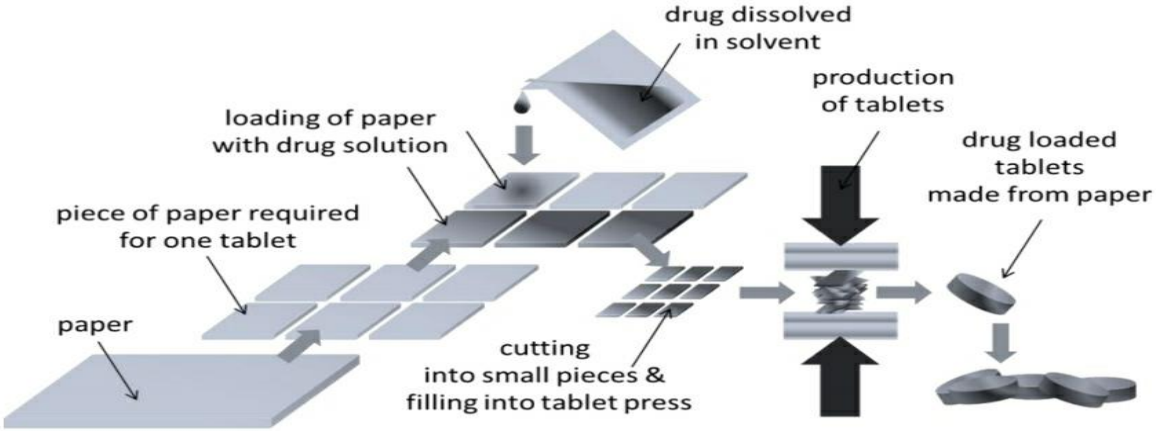


Figure 2.1 Scheme of production of drug-loaded tablets made from paper.

4. Direct Compression Method

It is the easiest way to manufacture tablets with conventional equipment and commonly available excipients. Moreover, a limited number of processing steps are involved in direct compression. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pre-treatment as in wet granulation unnecessary. Also, high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization are strongly affected by tablet size and hardness. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially super disintegrants like cross Carmel lose sodium, microcrystalline cellulose, cross povidone, sodium starch glycolate and partially substituted hydroxypropyl cellulose, effervescent agents (citric acid, sodium bicarbonate) and sugar-based excipients (dextrose, fructose, isomalt, maltitol, maltose, mannitol, sorbitol, starch hydrolyze, polydextrose, and xylitol).

5. Manufacture of tablets by direct compression method

As its name implies, direct compression involves direct compression of powdered materials into tablets without modifying the physical nature of the materials itself. The technology involved in this method assumes great importance in the tablet formulations, because it is often the cheapest means, particularly in the production of generics that the active substance permits. Direct compression avoids many of the problems associated with wet and dry granulations. Its successful application in tablet formulation rests on two fundamental issues:

1. The availability of suitable excipients
2. The availability of suitable machinery.

6. Pre-formulation Parameters

6.1 Organoleptic Properties:

The description of the drug substance should be the beginning of a preformulation program. The colour. Smell and taste of the new drug must be recorded. It is important to establish a standard terminology to describe these properties in order to avoid confusion among scientists using different terms to describe the same property. A table contains a list of descriptive terms 1o describe tastes and colour of pharmaceutical powders. The descriptive terminology must be Lsed to record the colour of the early batches of the new drug. Establishing appropriate specifications for later production can be

coated with a dye if the colour attributes are undesirable. Hand inspection of the reference drug and the sample drug was used to compare their physical qualities, The table contains the final results.

6.2 Solubility Studies:

The important phenomenon in pharmaceutical formulation is solubility which play very important role in the formulation of different dosage forms. "Solubility of compound in a particular solvent is defined as the concentration of a solute in a saturated solution at a certain temperature". If a compound has poor water solubility it may be associated with slow drug absorption. Most the formulation strategies for low solubility drugs are targeted at enhancing their dissolution rate and solubility by achieving their fine dispersion at absorption level. Nearly 40% of the new chemical entities currently being discovered are poorly water soluble drug. There are number of the method available for improvement of solubility. The solubility levels were determined, using the UV spectrometric method at 240nm. The UV spectrometric technique at 240 nm was used to calculate the solubility levels. In citrophosphate buffer pH 6.8 with 0.1% Sodium Lauryl Sulphate, ethanol, methanol, Dimethyl Sulfoxide (DMSO), and very slightly in water, the cilnidipine was easily soluble.

6.3 Formulation Development

Tablets made from paper can be obtained without any further excipients. Drug-loaded tablets made from paper can be obtained by pre-loading the respective paper with API and by subsequent compression of the drug-loaded films. Also, these tablets possessed good pharmaceutical quality, independent of the type of paper used. The release profiles of cilnidipine from the tablets were influenced by the type of paper and by the hardness of the tablets. The hardness of the tablets depends on the compression forces; thus, compression forces are a main parameter that influences the drug release profiles of cilnidipine from the tablets made from paper. These are the different papers like Kitchen roll, disposable handkerchief, coffee filter paper, and envelope paper which are used in preparation of smart film tablet. The data to determine the effect of on disintegration time and % drug release. The smart Film tablet which has much better data in comparison to marketed tablet.

7. Evaluation Parameters

1. Hardness:

This measures the degree of force (in kilograms, pounds, or in arbitrary units) needed to fracture a tablet. Besides the concentration of binders used and the compression force, the hardness of a tablet depends on

i. The characteristics of the granules to be compressed e.g., hardness and deformation under load.
ii. The type and concentration of lubricant used and
iii. The space between the upper and lower punches at the time of compression.

The crushing strength of tablets is usually checked using Monsanto or Stokes hardness tester, Strong-Cobb hardness tester and the Pfizer crushing strength tester. All are manually used. So, strain rate depends on the operator. Currently, electrically driven hardness testers such as those manufactured by SOTAX, Key, Van Kel, Erweka, Dr Schleuniger Pharmatron etc., are widely used to measure crushing strength of tablets. This equipment eliminates the operator variability encountered with manual hardness testers. Newer equipment with printers is also available. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet. Measurement is usually carried out using a minimum of ten tablets. It has been found that a linear relationship exists between crushing strength and the logarithm of compressional force, except at high forces. The strength of a cylindrical flat-faced tablet can be expressed as a tensile strength (Ts). This can be calculated as follows: $Ts = 2F/\pi Dt$

Where F is the force needed to fracture a cylindrical flat-faced tablet of thickness t along its diameter D.

2. Weight Variation:

The test for uniformity of weight is performed by weighing individually 20 tablets randomly selected from a tablet batch and determining their individual weights. The individual weights are compared with the average weight.The sample complies with IP standard if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. Coated tablets are exempted from these requirements but must conform to the test for content uniformity. To study weight variation individual weights (WI) of 10 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = (WA-WI)x 100/ WA

As the total tablet weight was 320 mg, according to IP 1996, out of ten tablets +5% variation can be allowed for not more than two tablets.

3. Thickness:

Tablet thickness is determined by the diameter of the die, the amount of fill permitted to enter the die cavity, the compaction characteristics of the fill material, and the force or pressure applied during compression. To manufacture

tablets of uniform thickness during and between batch productions for the same formulation, care must be exercised to employ the same factors of fill, die, and pressure.

The degree of pressure affects not only thickness but also hardness of the tablet; hardness is perhaps the more important criterion since it can affect disintegration and dissolution. Thus, for tablets of uniform thickness and hardness, it is doubly important to control pressure. Tablet thickness also becomes an important characteristic in packing operations and in counting of tablets using filling equipment which uses the uniform thickness of the tablets as a counting mechanism.

4. Friability:

This measures the resistance of tablets or granules to abrasion or fracture. The idea behind this test is to mimic the kind of forces, caused by phenomena such as collisions and sliding of tablets towards each other, which a tablet is subjected to during coating, packaging, handling, and shipping.A minimum of 20 tablets are dedusted, weighed and subjected to a uniform tumbling motion for a specified time. They are then dedusted and reweighed. The measure of abrasion/ friability loss is usually expressed as percentage loss in weight. It is calculated from the equation:

Friability loss (%) = Initial weight - Final weight / Initial weight x 100

The test is rejected if any tablet caps, laminates or breaks up in course of the test. As a rule of thumb, a maximum weight loss of not more than 1% generally is considered acceptable for most pharmaceutical products. Values of up to 2% or above have been reported in direct compression formulations.

The friability of tablets may be influenced by moisture content. Chewable tablets show a high friability weight loss compared to conventional compressed tablets. A number of instruments are available for friability tests but the most popular and most reliable is the Roche Friabilator.

5. Disintegration:

For tablets, the first important step towards drug dissolution is breakdown of the tablets into granules or primary powder particles, a process known as disintegration. All IP tablets must pass a test for disintegration, which is conducted in vitro using a disintegration test apparatus.The apparatus consists of a basket-rack assembly containing six open-ended transparent tubes of IP-specified dimensions, held vertically upon a 10-mesh stainless steel wire screen.During testing, a tablet is placed in each of the six tubes of the basket, and through the use of a mechanical device, the basket is raised and lowered in a bath of fluid (e.g. water, or as prescribed in the individual drug monograph) at 29 to 32 cycles per minute, the wire screen always below the level of the fluid. For most normal release tablets, the time permitted is 15 minutes.

Tablets are said to have disintegrated if no fragments (other than fragments of coating) remain on the screen, or if particles remain, they are soft without an unwetted core. Chewable tablets are not required to comply with the test.

Research has established that one should not automatically expect a correlation between disintegration and dissolution. However, since the dissolution of drug from the fragmented tablet appears to control partially or completely the appearance the drug in the systemic circulation, disintegration is still used as a guide by the formulator in the preparation of an optimum tablet formula and as an in-process control test to ensure batch to batch uniformity.
Factors affecting disintegration of tablets include:

i. Medium used
ii. Temperature of the test media
iii. Operator’s experience
iv. Nature of the drug
v. The diluent used in the formulation
vi. The type and concentration binder used
vii. Type and amount of disintegrant used including method of incorporation.
viii. The presence of excessive lubricants and overly mixed lubricants
ix. Compressional force used.

6. Drug Content/ Uniformity of Content:

Content uniformity test was developed to ensure content consistency of active drug substances within a narrow range around the label claim in dosage units. This test is crucial for tablets having a drug content of less than 2 mg or when the active ingredient comprises less than 2% of the total tablet weight.

By the IP method, 30 tablets are randomly selected, 10 of these tablets are assayed individually according to the method described in the individual monograph. Unless otherwise stated in the monograph, the requirements for content uniformity are met if the amount of active ingredient in nine (9) of the ten (10) tablets lies within the range of 85%to 115% of the label claim. The tenth tablet may not contain less than 75% or more than 125% of the labelled drug content.

If one or more dosage units do not meet these criteria, the remaining 20 tablets are assayed individually and none may fall outside of the 85% to 115% range for the batch to be accepted.

Various factors are responsible for the variable content uniformity in tablets. This may include:

i. Tablet weight variation.
ii. Uneven distribution of the drug in the powder or granules.
iii. Segregation of the powder mixture or granulation during formulation processes.

7. In-Vitro Dissolution:

This test measures the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions. It is intended to provide a step toward the evaluation of the physiological availability of the drug substances. In vitro dissolution test is performed using a variety of equipment/apparatus. The IP recommends three types of apparatus – the rotating basket, the rotating paddle and the flow-through cell. The static-basket magnetic stirrer assembly can also be used for this test. The rotating paddle method is generally more discriminatory than the basket method. The flow-through cell method is very useful particularly for

a. Poorly soluble active constituents (can use large volume to achieve sink conditions)
b. Enteric-coated products (can easily change between different pH fluids)
c. Modified release products.
d. The dissolution medium for each drug is available in the individual drug monograph. For basic drugs, acidic media are used (e.g. 0.1 M hydrochloric acid) while alkaline media are used for acidic drugs (e.g. alkaline buffers). For drugs with non-ionizing molecules, water is recommended.
e. Dissolution rate test is performed at 37 ± 1 °C. Samples are removed from the dissolution chamber at periodic intervals and analyzed for drug content using a spectrophotometer. Dissolution samples removed for assay should be filtered to remove particles of drugs present, and to exclude tablet excipients that might otherwise interfere with the assay. Non-absorbent filter papers are recommended.
f. Most commonly, the results of dissolution tests are expressed in terms of the time required to release some percentage of labelled amount of drug from the dosage form. This approach is reported to be particularly useful for quality control purposes once the dissolution characteristics of a drug and dosage form are well understood.

For tablet dosage form design purposes, and for critical product comparison, however, the time required for substantially complete 80 to 90% release or amount released versus time profiles are the most desired approach.

While in vitro dissolution experiment may not correlate perfectly with in vivo bioavailability, the concept of dissolution efficiency proposed by Kahn and Rhodes could be employed to assess the most probable in vivo performance of a tablet formulation.

Dissolution test is not designed to measure the efficacy or safety of the tablet being tested. Both the effectiveness and safety of a specific dosage form must be demonstrated, initially, by means of appropriate in vivo studies and clinical evaluation.

RESULTS AND DISCUSSION

1. Identification of drug

1) ldentification of drug by Melting point:

Melting point was determined using capillary fusion method and its results are shown in table 5.1.

Table 3.1 Melting point

Theoretical range	Observed value
105°C – 110°C	108°C-110°C

2) Calibration curve by using UV Spectroscopy:

The absorbance of the prepared solutions was determined using methanol as blank at the wavelength maximum was found to be 240nm. At this wavelength maximum calibration graph was drawn between absorbance (on Y-axis) and concentration (on X-axis).

Table 3.2 Absorbance of UV spectroscopy

Concentration (µg/ml)	Absorbance [Mean(n=3) ±SD]
0	0
2	0.248±0.03
4	0.383±0.02
6	0.532±0.01

8	0.659±0.05
10	0.809±0.08

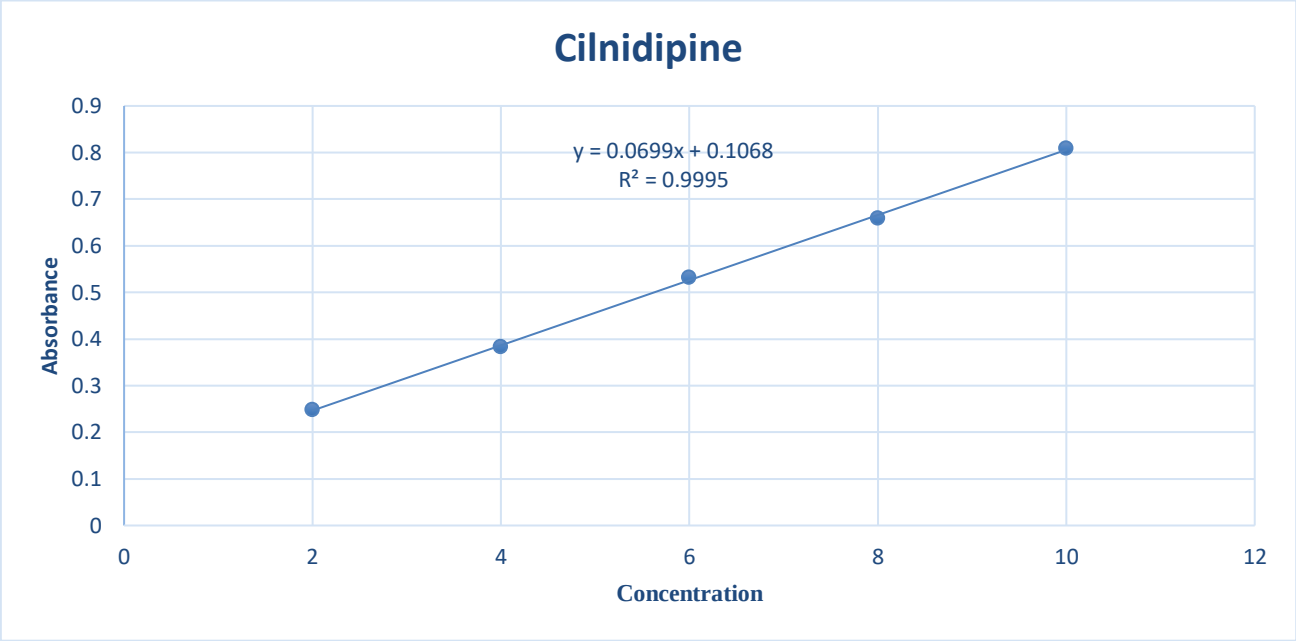


Figure 3.1 Standard calibration curve of cilnidipine

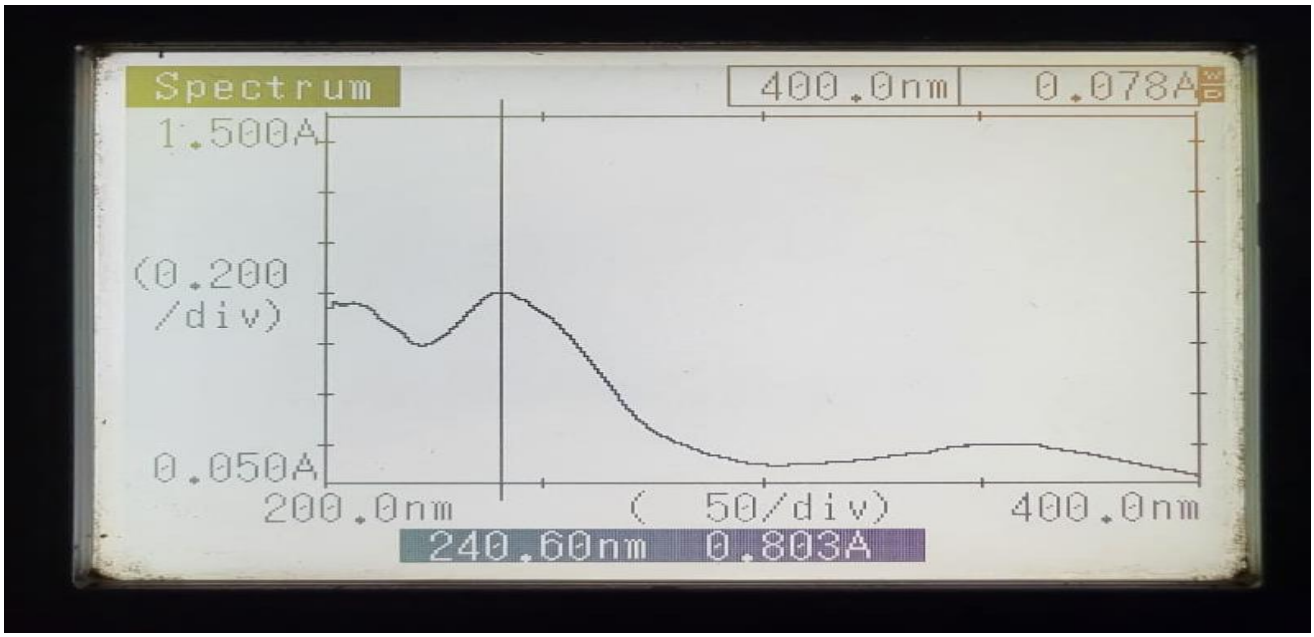


Figure 3.2. UV spectra of Cilnidipine.

3) Infrared Spectroscopy (FT-IR):

Fourier transform infrared spectroscopic studyan FT-IR spectrumof pure drug was compared with references spectra of Cilnidipine and the possibility of functional group present in Cilnidipine was concluded. From study data we estimate that drug is Cilnidipine.

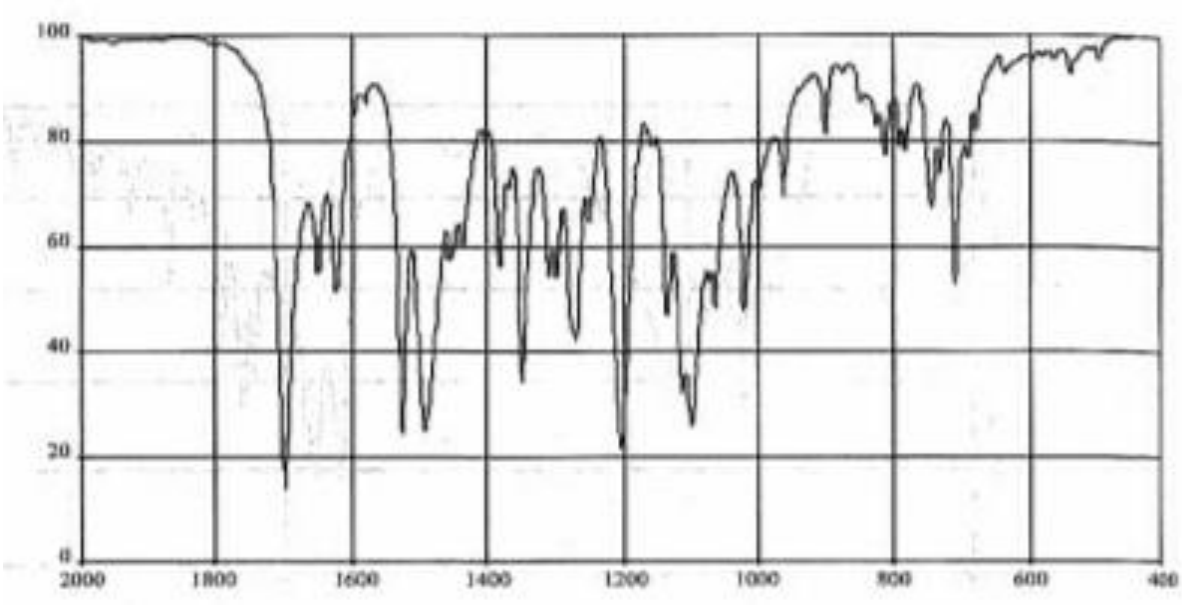


Figure 3.3 FT-IR IP spectra of cilnidipine.

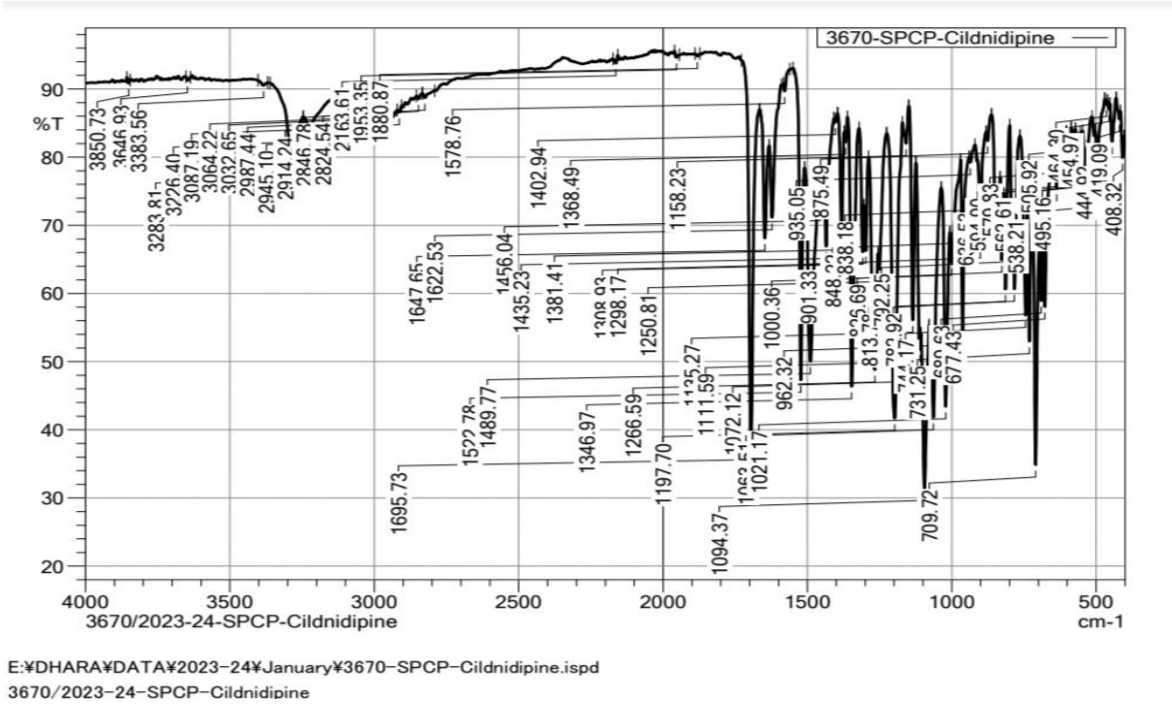


Figure 3.4 FT-IR spectra of cilnidipine

Table 3.3 Interpretation of FT-IR spectra

Functional group	Standard frequency(cm-1)	Observation frequency of drug (cm-1)
C-N Aromatic 2° amine	1020-1250	1021.17
N-O	1360-1556	1346.97
C=O	1630-1980	1647.65
-OCH3	2815-2950	2914.24
C-O	1200-1225	1266.59
N-H Aromatic 2° amine	3250-3400	3283.81

2. Organoleptic properties:

Tablet 5.4. Organoleptic properties of Cilnidipine.

Sr.No.	Properties	Standard	Sample
1.	State	Solid	Solid
2.	Color	Yellow	Yellow
3.	Odor	Odorless	Odorless
4.	Taste	Tasteless	Tasteless
5.	Solubility	Soluble in ethanol, methanol and insoluble in water	Soluble in ethanol, methanol and insoluble in water

3. Solubility:

Tablet 5.5. Solubility of Cilnidipine.

Sr. No.	Name of the Solvent	Solubility (mg/ml)
1.	Dimethyl Sulfoxide (DMSO)	0.7288 mg/ml
2.	Ethanol	0.822 mg/mi
3.	Methanol	0.878 mg/ml
4.	Water	0.0059 mg/ml
5.	Citrophosphate buffer pH 6.8 with 0.1% Sodium Lauryl Sulphate	0.928 mg/ml

Solubility of Cilnidipine were shown in the table 5.5. Cilnidipine drug freely soluble in ethanol and methanol. Solubility increases in the citrophosphate buffer pH 6.8 with 0.1% sodium luryal sulphate.

4. Evaluation parameters:

The tablet formulations were subjected to evaluation of physical parameters which include uniformity of weight. Thickness, hardness, friability. Drug content of the tablets. The results of which were given in the table 5.4.

Tablet 4.1 Evaluation parameters [mean n=3 ± SD].

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (gm/cm²)	Friability (%)	Disintegration Time (sec)	Drug content (%)
Disposable handkerchief paper tablet (T1)	250.8±0.86	3.01±0.4	2.4±0.2	0.19±0.1	11±2	98.89±0.47
Coffee Filter paper tablet (T2)	250.2±0.93	4.02±0.3	3.1±0.3	0.28±0.3	14±1	99.17±0.24
Kitchen Roll paper tablet (T3)	250.5±0.72	4.08±0.3	2.8±0.2	0.37±0.2	17±2	98.1±0.22
Envelope paper tablet (T4)	250.7±0.80	3.07±0.2	3.3±0.4	0.25±0.1	16±3	98.14±0.42

The post-compression parameters such as hardness, friability, drug content, and tablet weight variation are presented in Table 5.4. The hardness test indicated good mechanical strength with non-significant differences in all formulation. All the tablets showed good mechanical resistance. As indicated by the friability test where it was less than 1% for all tablets. Drug content was found to be consistent and almost uniform in all tablet formulations (> 98%) and no significant statistical mass variability was observed in the produced tablets. Therefore, our results, as indicated by the post-

compression parameters presented in Table 5.4, showed that an excellent degree of uniformity was achieved for all prepared tablet formulations out of all batches falls under our require specifications.

5. In-Vitro Dissolution Study:

Table 5.1 In-vitro drug release study

Sr. No.	Time (min)	% Drug releaseT1 tablet	% Drug release T2 tablet	% Drug release T3 table	% Drug release T4 tablet	Marketed tablet (M)
1.	0	0	0	0	0	0
2.	1	46.87%	38.88%	32.85%	42.97%	1.65%
3.	2	78.90%	69.93%	71.53%	66.78%	5.07%
4.	3	83.53%	80.32%	82.69%	80.92%	13.32%
5.	4	92.43%	90.35%	89.77%	90.11%	22.56%
6.	5	99.21%	98.49%	95.83%	96.36%	36.71%

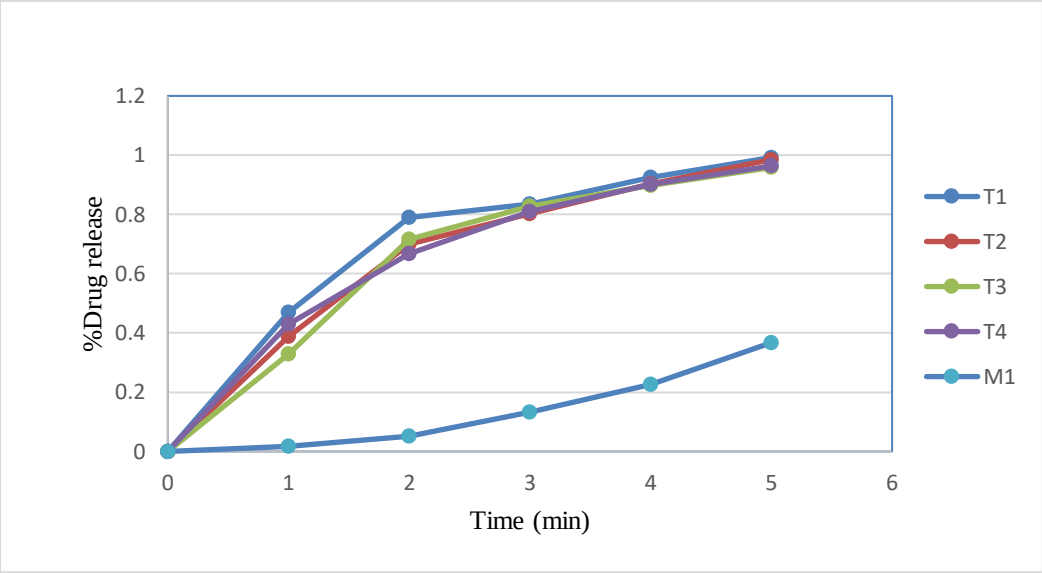


Figure 5.1 In- vitro drug release study.

The data for in-vitro drug release was shown in table 5.1 and dissolution profiles are shown in figure 5.1. The in-vitro dissolution study of all 4 tablets shows more than 90% drug release within 5 minutes. The maximum dissolution was observed in T1 tablet (99.21% drug release within 5 min.). So, results showed that the tablet T1 Containing higher concentration of Cilnidipine exhibited higher dissolution.The results shows that the percentage of drug dissolved from T1 tablet was 99.21% compared to only 36.71% for the marketed tablet within 5 min. It is evident from the results that smart film tablet exhibited increased dissolution compared to that of marketed tablet.

Figure 5.6. (a) & (b) are disposable handkerchief paper tablets. (c) & (d) are coffee filter paper tablets.

SUMMARY & CONCLUSION

Drug-loaded tablets made from paper can be obtained by pre-loading the respective paper with API and by subsequent compression of the drug-loaded films. The result can be conducted that the smart film tablet, increase the dissolution rate and decrease the disintegration time of cilnidipine BCS class-II drug than the marketed formulation. Based on these results it can be concluded that tablets made from paper represent a novel, promising drug delivery system for the delivery of poorly soluble API and also for the production of individualized pharmaceutical oral drug products. Based on the results it can therefore be concluded that smart film tablets are an industrially feasible formulation approach for improved oral delivery of poorly soluble drugs.

These tablets possessed good pharmaceutical quality, independent of the type of paper used. The release profiles of cilnidipine from the tablets were influenced by the type of paper and by the hardness of the tablets. These are the different papers like Kitchen roll, disposable handkerchief, coffee filter paper, and envelope paper which are used in preparation of smart film tablet. The data to determine the effect of on disintegration time and % drug release. The smart film tablet which has much better data in comparison to marketed tablet.

The result of a disintegration of smart film tablet are obtained in disposable handkerchief paper tablet is 11sec, Coffee filter paper tablet is 14sec, Kitchen roll paper tablet is 17sec, Envelope paper tablet is 16sec. In-vitro % drug release data of disposable handkerchief paper tablet is 99.11%, coffee filter paper tablet is 98.49%, kitchen roll paper tablet is95.83%, envelope paper tablet is 96.36% in 5 min. In-vitro % drug release data of marketed tablet is 36.71% in 5min.

So, we conclude that from all the data disposable handkerchief paper tablet is effectively increase the dissolution rate of the drug cilnidipine which is better than other different paper tablet. And also conclude that all smart film tablet which increase the dissolution rate other than the marketed tablet.

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