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FORMULATION AND IN-VITRO EVALUATION OF NIFEDIPINE SUBLINGUAL TABLETS

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ABSTRACT
Nifedipine is a medication used to manage angina, high blood pressure, Raynaud's phenomenon, and premature labor. It is one of the treatments of choice for Prinzmetal angina. It may be used to treat severe high blood pressure in pregnancy. Its use in preterm labor may allow more time for steroids to improve the baby's lung function and provide time for transfer of the mother to a well-qualified medical facility before delivery. In the present work, an attempt has been made to develop Sublingual tablets of Nifedipine chitosan, Locust bean gum and crospovidone were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations NDPN4 formulation showed maximum % drug release i.e., 98.73 % in 8 min hence it is considered as optimized formulation. The NDPN4 formulation contains locust bean gum as super disintegrate in the concentration of 15 mg.

Key words: Nifedipine, chitosan, Locust bean gum and Croscarmellose sodium

INTRODUCTION

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug [1]. The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large-scale economic manufacture, have led to a steady decline in the prescribing of powders and pills. Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world [2]. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet [3]. All medicaments are available in the Tablet form except where it is difficult to formulate or administer.

The advantages of the Tablet dosage form are:

- ✓ Cost is lowest of all oral dosage form.
- ✓ Lighter and compact.
- ✓ Easiest and cheapest to package and strip.
- ✓ Easy to swallowing with least tendency for hang-up.
- ✓ Sustained release product is possible by enteric coating.

Disadvantages of Tablet dosage form are:

- ✓ Difficult to swallow in case of children and unconscious patients.
- ✓ Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

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- ✓ Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

Advantages of sublingual drug delivery system

- ✓ Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
- ✓ A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- ✓ The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- ✓ Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- ✓ They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Disadvantages of sublingual drug delivery system

- ✓ Sublingual administration of drugs interferes with eati ng, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- ✓ Although this site is not well suited to sustained-delivery systems.
- ✓ Sublingual medication cannot be used when a patient is uncooperative or unconscious.
- ✓ The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication [4, 5].

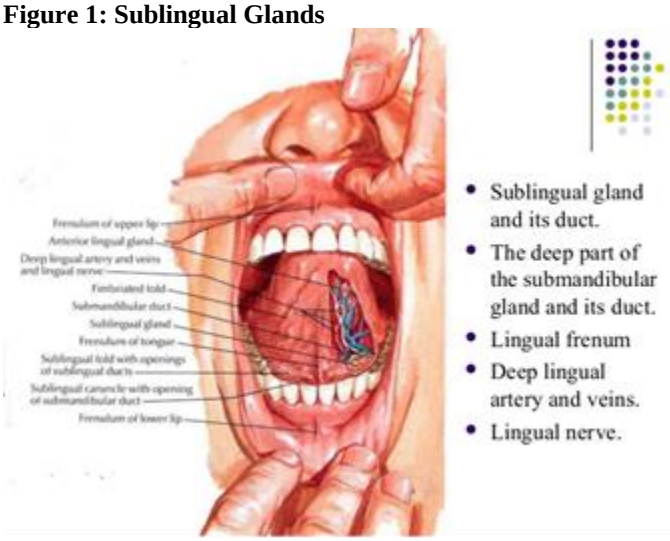
Suitability of drug for preparation of sublingual tablet

No bitter taste. Dose lowers than 20 mg, e.g. nifedipine. Small to moderate molecular weight. Good stability in water and saliva. Partially no ionized at the oral cavities pH. Undergoing first pass effect e.g. ketotifen fumarate. Many drug properties could potentially affect the performance of sublingual tablets like solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug. Some drugs undergoes extensive first pass metabolism which results in poor bioavailability of its oral dosage forms, that kind of drugs are suitable for sublingual dosage form [6]. Drugs that are unstable in parenteral preparation are suitable for sublingual dosage form. Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, antiemetics, vitamins, minerals and vaccines.

Sublingual Glands

Sublingual glands are alsoknown as the salivary glands which are present in the floor of mouth underneath the tongue. These glands produce mucin and help to promote the production of saliva. Because of the secretions of the glands, the interior area of the mouth is kept lubricated, which is necessary for chewing and swallowing food. The lubrication and binding functions of the sublingual glands cannot be underestimated. A secretion from the glands mix with food as it is chewed, making the material slippery and easily swallowed. Because of the saliva content of the masticated food, it can move without difficulty into the throat and on to the digestive tract. Low levels of saliva production can make the process of swallowing much more difficult and will increase the potential for food to lodge in the throat [7]. The drug is released in to saliva and its subsequentspreading may cause the drug to be absorbed ac ross the oral cavity.

Figure 1: Sublingual Glands



Sublingual tablets

They are to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein. Thus absorption through oral cavity avoids first pass metabolism [8]. The tablets are usually small and flat, compressed lightly to keep them soft. The tablet must dissolve quickly allowing the API to be absorbed quickly.

Fast disintegrating sublingual tablets (FDT)

FDT is defined as a solid dosage form that contains medicinal substances and disintegrates rapidly (within few seconds) without water when kept on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT

[9]. FDTs also are also called as Orodispersible tablet, mouth-dissolving, quick-dissolving, fast-melt, and freeze-dried wafers. Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties and in situations where potable liquids are not available [10]. Direct compression is one of the techniques which require the incorporation of a superdisintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. Compared to conventional dosage form the drug dissolution, its absorption as well as onset of clinical action and its bioavailability may be significantly greater [11].

Factors Affecting the Sublingual Absorption

- Solubility in Salivary Secretion
- Binding to Oral Mucosa
- pH and pKa of The Saliva
- Lipophilicity of Drug
- Thickness of Oral Epithelium

MATERIALS

Nifedipine, Microcrystalline cellulose, Chitosan, Locust bean gum, Crospovidone, Magnesium stearate, Talc.

METHODOLOGY

Preformulation Studies

The goals of the preformulation study are:

- ❖ To establish the necessary physicochemical characteristics of a new drug substance.
- ❖ To determine its kinetic release rate profile.
- ❖ To establish its compatibility with different excipients [12].

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

Determination of absorption maximum (λ_{max}):

Absorption maximum is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Nifedipine was weighed accurately 10 mg and transferred to 100 ml volumetric flask, dissolved in phosphate buffer pH 6.8 and the final volume was made up to 100 ml with phosphate buffer pH 6.8 to get a stock solution (100µg/ml). From the stock solution, 1 ml was pipette out in 10 ml volumetric flask and the final volume was made up to 10 ml with phosphate buffer PH 6.8 to get 10µg/ml. Then this solution was scanned at 200-400nm in UV-Visible double beam spectrophotometer (UV-3200, Labindia, India) to get the absorption maximum (λ_{max}).

Construction of Nifedipine calibration curve with phosphate buffer pH 6.8:

100mg of Nifedipine was dissolved in 100ml of phosphate buffer pH 6.8 to give a concentration of 1mg/ml (1000µgm/ml). From the above standard solution (1000µgm/ml) 10 ml was taken and diluted to 100ml with phosphate buffer pH 6.8 to give a concentration of 100µgm/ml [13]. From this stock solution aliquots of 0.1,0.2,0.3,0.4,0.5 and 0.6ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with phosphate buffer PH 6.8 to produce concentration of 1,2,3,4,5 and 6 µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 286 nm.

Drug- excipient compatibility studies by FT-IR:

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

Flow properties:

Angle of Repose:

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula:

$\Theta = \tan^{-1} H/R$

Θ=angle of repose, H=height of powder cone, R=radius of powder cone

Angle of Repose less than 30^0 shows the free-flowing property of the material.

Loose bulk Density (LBD):

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below: $Df = M / Vp$

Df = bulk density, M = weight of sample in grams, Vp = final volume of powder in cm^3

Tapped density (TD):

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

Do = M /Vp

Do = Tapped density, M = weight of sample in grams, Vp = final volume of powder after tapping in cm^3

Carr's consolidation index:

The Carr index is an indication of the compressibility of a powder. This is calculated by the formula

$$C = \frac{(\rho b - \rho t)}{\rho b} \times 100$$

Where, ρ_b is the bulk density, ρ_t is the tapped bulk density

A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Hausner's ratio:

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula

$$H = \rho_{b/} \rho_b$$

ρ_b is the bulk density, ρ_b is the tapped bulk density

Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Formulation of Sublingual tablets of Nifedipine:

Preparation of tablets:

Composition of Nifedipine Sublingual Tablet by direct compression. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 8mm flat punch, B tooling. Each tablet contains 30 mg Nifedipine and other pharmaceutical ingredients. Total weight of tablet was found to be 150 mg.

Table 1: Composition of various tablet formulations

Ingredients	NDPN1	NDPN2	NDPN3	NDPN4	NDPN5	NDPN6	NDPN7	NDPN8	NDPN9
Nifedipine(mg)	30	30	30	30	30	30	30	30	30
Chitosan (mg)	15	30	45	-	-	-	-	-	-
Locust bean gum (mg)	-	-	-	15	30	45	-	-	-
Crospovidone	-	-	-	-	-	-	15	30	45
Magnesium Stearate(mg)	3	3	3	3	3	3	3	3	3
Talc(mg)	3	3	3	3	3	3	3	3	3
MCC (mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	150	150	150	150	150	150	150	150	150

Post compression parameters

Evaluation of tablets

Shape and colour:

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by,

$$F = \frac{[W(initial) - W(final)]}{W(initial)} \times 100$$

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The % deviation in weight variation is shown in table.

Drug Content estimation:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Four tablets were weighed and crushed in the mortar [14, 15]. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 286nm using UV Visible spectrophotometer (Lab India, UV-3200).

***In -vitro* dissolution studies:**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Nifedipine by measuring absorbance at 286 nm [16]. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8.

RESULTS AND DISCUSSION

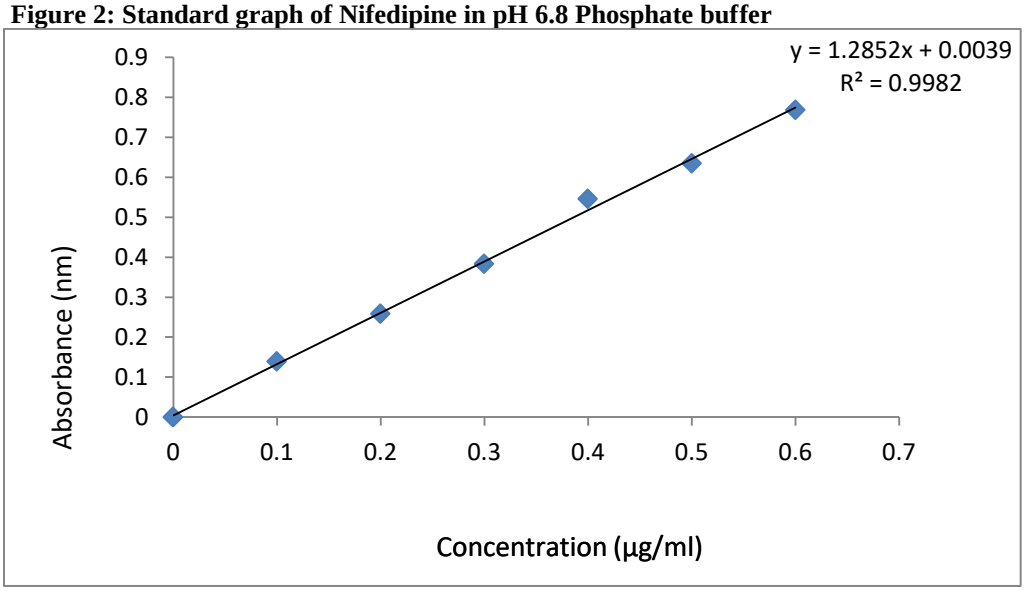
Standard Calibration curve of Nifedipine:

Table 2: Concentration and absorbance obtained for calibration curve of Nifedipine In pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance (at 286 nm)
1	**0**	**0**
2	**0.1**	**0.139**
3	**0.2**	**0.258**
4	**0.3**	**0.383**
5	**0.4**	**0.546**
6	**0.5**	**0.635**
7	**0.6**	**0.769**

It was found that the estimation of Nifedipine by UV spectrophotometric method at λ_{max} 286 nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 1- 6µg/ml. The regression equation generated was y = 1.2852x + 0.0039, R^2 = 0.998.

Figure 2: Standard graph of Nifedipine in pH 6.8 Phosphate buffer



Evaluation Parameters for Sublingual Tablets of Nifedipine:

FTIR

Figure 3: FTIR Spectrum of pure drug

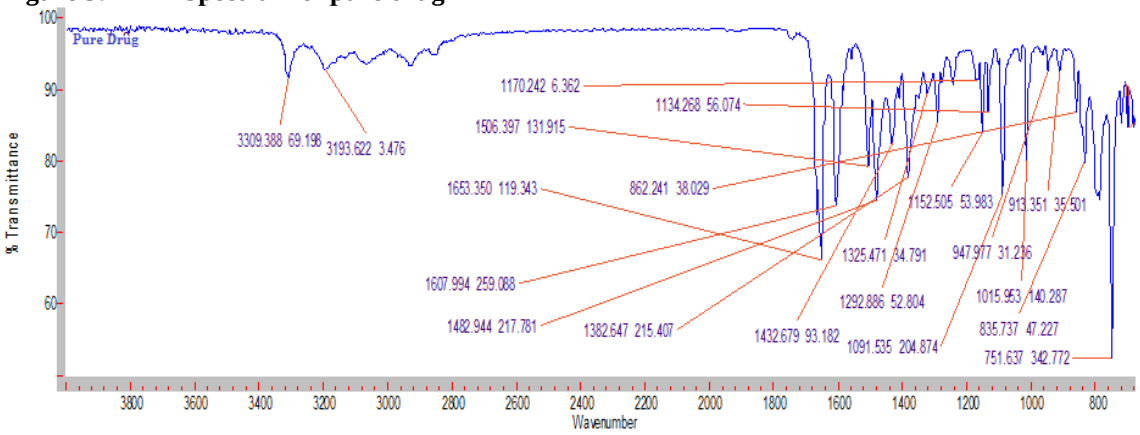
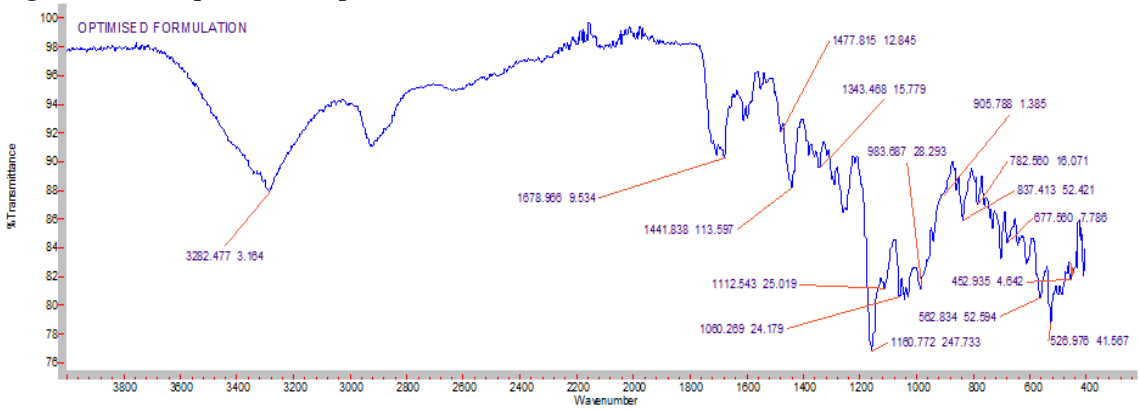


Figure 4: FTIR spectrum of optimized formulation



Pre-compression parameters:

Table 3: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Θ)
NDPN1	**0.50**	**0.53**	**14.09**	**1.16**	**23.68**
NDPN2	**0.48**	**0.55**	**15.38**	**1.14**	**24.87**
NDPN3	**0.49**	**0.54**	**13.57**	**1.20**	**25.49**
NDPN4	**0.48**	**0.56**	**15.92**	**1.12**	**26.57**
NDPN5	**0.50**	**0.53**	**16.12**	**1.19**	**23.76**
NDPN6	**0.46**	**0.59**	**17.08**	**1.20**	**24.87**
NDPN7	**0.49**	**0.56**	**14.74**	**1.08**	**25.63**
NDPN8	**0.46**	**0.57**	**16.82**	**1.17**	**26.68**
NDPN9	**0.47**	**0.59**	**15.76**	**1.19**	**27.42**

Post compression Parameters:

Table 4: Post-Compression parameters

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
NDPN1	153	2.1	1.44	62	0.52	97.27
NDPN2	156	2.2	1.62	64	0.54	98.36
NDPN3	149	2.3	1.59	66	0.52	99.81

NDPN4	153	2.5	1.47	65	0.55	98.19
NDPN5	152	2.7	1.40	67	0.57	97.30
NDPN6	153	2.4	1.57	68	0.56	99.04
NDPN7	154	2.3	1.63	62	0.58	98.38
NDPN8	155	2.5	1.41	66	0.57	97.12
NDPN9	156	2.4	1.54	64	0.54	99.57

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 4. The average weight of the tablet is approximately in range of 149 to 156 mg, so the permissible limit is ±10% (=150mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data were shown in Table 4. The results showed that the hardness of the tablets is in range of 2.1 to 2.7 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table 4. The result showed that thickness of the tablet is raging from 1.40 to 1.63.

Friability:

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 4. The average friability of all the formulations lies in the range of 0.52 to 0.58% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro disintegration time:

Tablets of each batch were evaluated for in vitro disintegration time and the data were shown in the Table 4. The results showed that the disintegration time of prepared tablets were in the range of 62 to 68 seconds.

Assay:

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.12-99.81%.

In-vitro Dissolution studies:

In-vitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 8 min.

Figure 5: Dissolution profile of formulations prepared with chitosan as super disintegrate

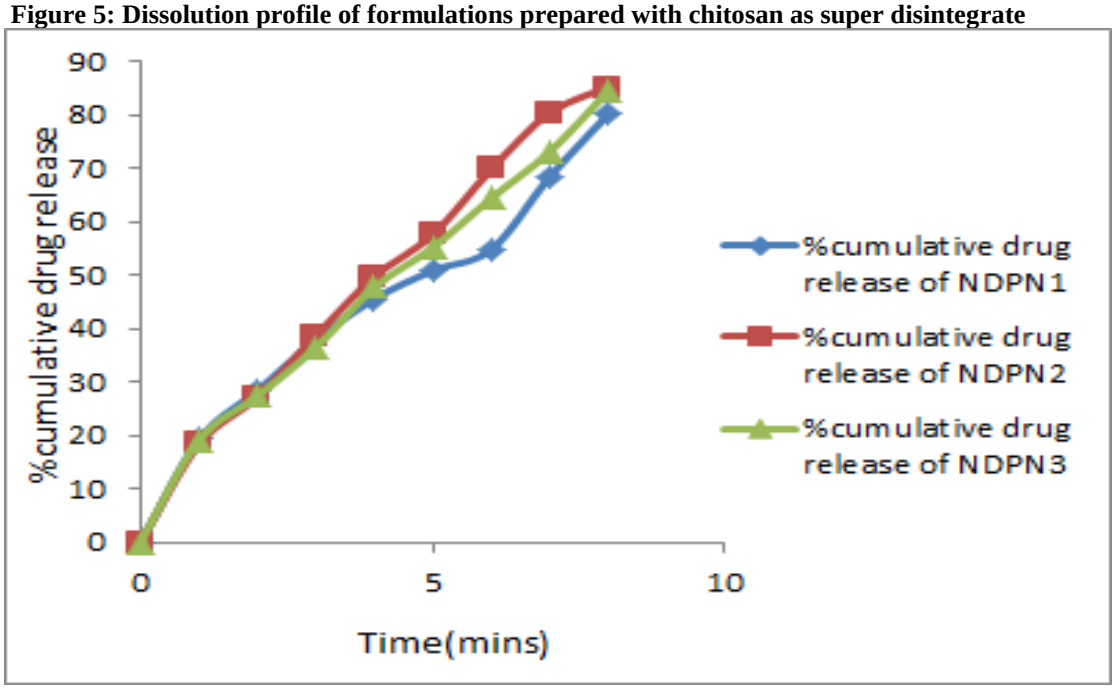


Figure 6: Dissolution profile of formulations prepared with Locust bean gum as super disintegrate

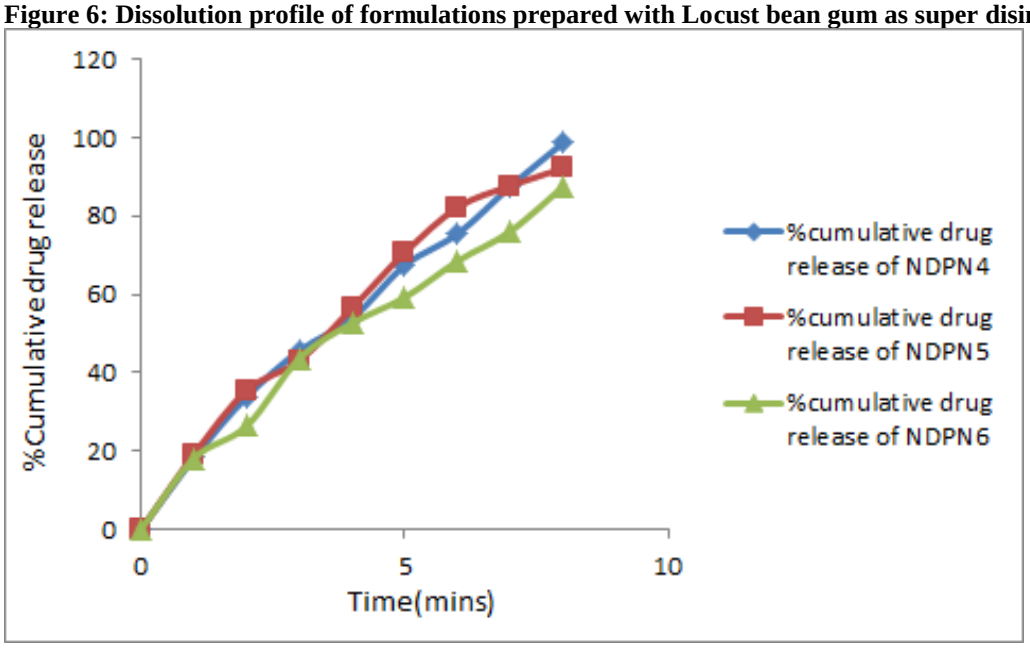
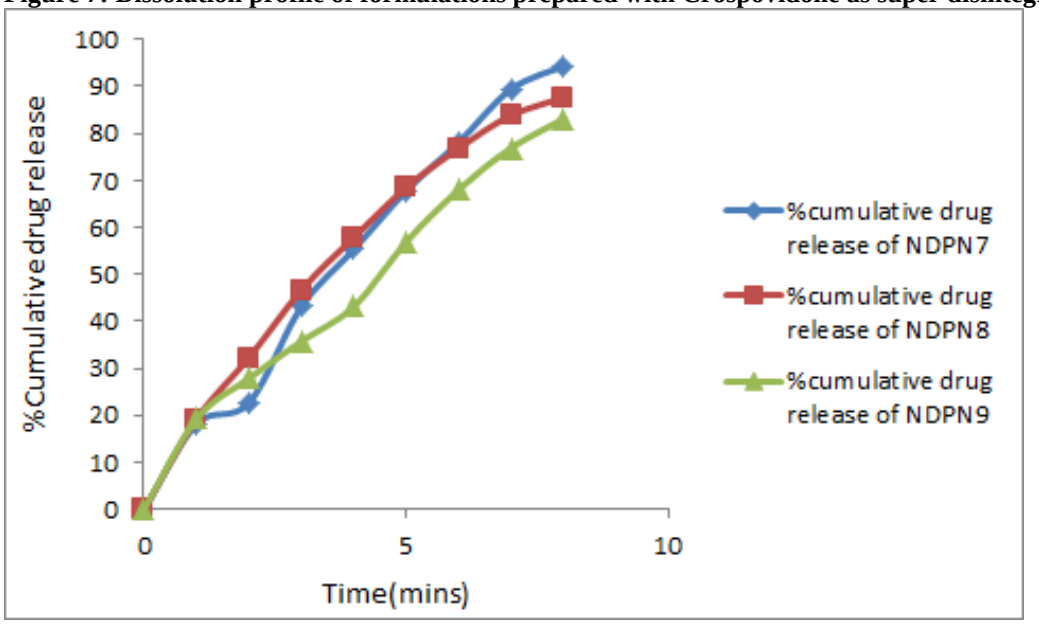


Figure 7: Dissolution profile of formulations prepared with Crospovidone as super disintegrate



CONCLUSION

In the present work, an attempt has been made to develop Sublingual tablets of Nifedipine. In the present work chitosan, Locust bean gum and Crospovidone were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations NDPN4 formulation showed maximum % drug release i.e., 98.73 % in 8 min hence it is considered as optimized formulation. The NDPN4 formulation contains locust bean gum as super disintegrate in the concentration of 15 mg.

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