World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

FORMULATION AND EVALUATION OF ISOSORBIDE DINITRATE BUCCAL TABLETS

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Received: 26-11-2025 / Revised Accepted: 28-11-2025 / Published: 30-11-2025

ABSTRACT

In the present study, an attempt was made to prepare Buccal tablets of Isosorbide dinitrate, in order to overcome bioavailability problems, to reduce dose dependent side effects. Buccal tablets containing the drug were prepared by direct compression method using combinations of polymers (such as Guar gum, Carbopol 940, Xanthan Gum and Pectin). Estimation of Isosorbide dinitrate was carried out spectrophotometrically at 405 nm. The Buccal tablets were evaluated for various physical and biological parameters, drug content uniformity, *in-vitro* drug release, drug-excipient interactions (Infrared Red). FTIR spectroscopic studies indicated that there are no drug-excipient interactions. The formulations F12 (containing 45mg of Pectin) were found to be promising, which showed maximum drug release within 8hrs. These formulations have displayed good bioadhesion strength (29.12±1.18 gm respectively).

Keywords: Isosorbide dinitrate, Pectin, Buccal Tablets, FTIR.

INTRODUCTION

When gum tragacanth was combined with dental adhesive powder to apply penicillin to the oral mucosa in 1947, bioadhesive drug delivery formulations were first used. The use of mucoadhesive drug delivery systems to administer medicinal drugs has grown in popularity in recent years. Some medications are ineffective because of reduced bioavailability, gastrointestinal intolerance, irregular and unpredictable absorption, or pre-systemic clearance of alternative possible routes of delivery. The study of mucosal medication delivery has accelerated due to recent advancements in drug delivery. Oral, buccal, ocular, nasal, and pulmonary routes are among them. medicine delivery methods that use the bioadhesion of certain polymers—which become sticky when hydrated—to target a medicine to a specific area of the body for a prolonged amount of time are known as mucoadhesive drug delivery systems. Both local and systemic medication bioavailability greatly benefit from the capacity to keep a delivery system in place at a specific spot for a long time. Recent years have seen a lot of attention in the pharmaceutical aspects of mucoadhesion because it offers the potential to prevent medication degradation by gastrointestinal contents or hepatic first-pass inactivation.[1,2]

By offering an alternate method of drug administration through the buccal mucosa—the inner lining of the cheek—baccal drug delivery devices constitute a substantial breakthrough in the fields of pharmacology and therapeutics. This approach is a desirable choice for patients and healthcare professionals alike since it has a number of benefits over conventional oral and parenteral methods. Because of its high vascularization, the buccal mucosa allows for quick and effective medication absorption straight into the bloodstream, avoiding the gastrointestinal tract and first-pass hepatic metabolism. This feature is especially helpful for medications that are heavily metabolized by the liver, unstable in the stomach's acidic environment, or poorly absorbed from the gastrointestinal system. As a result, buccal medication administration can decrease systemic adverse effects, increase bioavailability, and lower dose needs. In buccal medication administration, a range of dosage forms are employed, such as tablets, films, patches, and gels. These formulations are made to stick to the buccal mucosa and deliver the medication gradually over a certain amount of time. Mucoadhesive polymers are frequently added to dosage forms to increase their adherence and retention duration, guaranteeing steady and extended

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How to Cite this Article: Sohel Rana, FORMULATION AND EVALUATION OF ISOSORBIDE DINITRATE BUCCAL TABLETS, World J Pharm Sci 2025; 13(04): 78-88; https://doi.org/10.54037/WJPS.2022.100905

drug release. Patients with dysphagia, such as the elderly, young children, and people with specific medical problems, benefit greatly from the buccal route. Additionally, it provides a non-invasive substitute for medications that are normally given by injection, improving patient comfort and compliance. Additionally, by delivering high medication concentrations straight to the site of action, buccal drug administration can offer targeted therapy for oral problems such periodontal diseases, fungal infections, and mouth ulcers.[3-5]

The goal of new drug administration methods is to boost the medication's therapeutic effectiveness. Using bioadhesive dosage forms for buccal medication delivery provides a unique way to administer drugs. Numerous medication candidates have been effectively delivered systemically using this method. By delivering the medication through the buccal route, issues including high first-pass metabolism and drug degradation in the hostile gastrointestinal environment can be avoided. Furthermore, because drug absorption may be quickly stopped in situations of toxicity by withdrawing the dosage form from the buccal cavity, buccal drug administration provides a simple and safe way to utilize drugs. For people who cannot take their medications orally, it is an alternate method of administration. For buccal distribution, adhesive mucosal dosage forms such as adhesive tablets, sticky gels, and adhesive patches are thus advised[6]. For systemic drug delivery, transmucosal routes—that is, the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities—offer clear benefits over peroral administration. These benefits include avoiding presystemic clearance in the GI tract, avoiding the first pass impact, and, depending on the medicine, having a superior enzymatic flora for drug absorption[7]. An efficient nitrate for preventing angina pectoris and reducing preload in the treatment of congestive heart failure is isosorbide dinitrate.[8]

MATERIALS

Isosorbide dinitrate was procured from Spansules Pharmatech Pvt Ltd, Lactose, Guar gum, Carbopol 940, Xanthan Gum, Pectin, PVP K30 were procure from oxford pharma labs, Mannitol, Talc, Magnesium stearate were procured from lobachempharma ltd.

METHODOLOGY

Preformulation Studies: [9-12]

Preformulation testing is the initial phase in the improvement of dose types of a drug substance. It is one of the critical essential being developed of any drug delivery system. It tends to be characterized as an examination of physical and synthetic properties of a medicament substance alone and when joined with excipients. Characterization of the medicament is an essential advance at the preformulation period of item improvement taken after by concentrate the properties of the excipients and their similarity. The general goal of Preformulation testing is to produce data valuable to the formulator in creating steady and bio-available measurements frames, which can be mass- produced. The following are the various Preformulation studies.

Solubility:

Solubility of Isosorbide dinitrate was determined in 0.1N HCl, pH 7.4 and pH 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Isosorbide dinitrate in different beakers containing the solvents. The mixtures were shaken for 48hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 405 nm.

Drug-Excipient Compatibility Studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation studies must generate the needed information.

FT IR Studies:

Physical compatibility studies were assured by IR studies. The IR spectrums of the mixed powders were taken by preparing Potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minimal (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards.

Identification of Isosorbide dinitrate

PREPARATION OF REAGENTS

Phosphate buffer pH 6.8 for 1000ml.

Weigh the quantity of 28.80gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate and then add one by one in 1000 ml volumetric flask by mixing with a glass rod make up to the 100ml mark with the distilled water and sonicate the solution in ultra sonicator for 20 minutes.

Determination of UV spectrum of Isosorbide dinitrate:

10mg of Isosorbide dinitrate was dissolved in 6.8pH buffer to get a stock solution of 1000 µg/ml concentration. From this 1ml solution was withdrawn and diluted to 10ml to get a concentration of 100µg/ml (SS-II). From this stock solution pipette out 1 ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of Standard Calibration Curve of Isosorbide dinitrate

Preparation of Standard Solution :

Standard stock solution of Isosorbide dinitrate was prepared. 10 mg of Isosorbide dinitrate was accurately weighed into 10ml volumetric flask and dissolved in small quantity of methanol. The volume was made up with 6.8pH buffer to get a concentration of 1000µg/ml (SS-I). From this 1ml solution was withdrawn and diluted to 10ml to get a concentration of 100µg/ml (SS-II).

Preparation of working standard solutions:

Further, from (SS-II) aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml and 1.2ml were pipette into 10ml volumetric flasks. The volume was made up with 6.8pH buffer to get the final concentrations of 2-12 µg/ml respectively. The absorbance of each concentration was measured at 405 nm.

FLOW PROPERTIES:

Bulk Density (Db): It is the proportion of aggregate mass of powder to the mass volume of powder. It was estimated by pouring the measured powder (went through standard sieve#20) into an estimating barrel and the underlying volume was noted. This underlying volume is known as the mass volume. From this, the mass thickness is computed by the equation specified beneath. It is communicated in g/cc and is given by

$$Db = m/Vo$$

Tapped density (Dt):

It is the proportion of aggregate mass of powder to the tapped volume of powder. The volume was estimated by tapping the powder for 500 times. At that point the tapping was improved the situation 750 times and the tapped volume was noticed (the contrast between the two tapped volumes ought to be under 2%). In the event that it is over 2%, tapping is proceeded for 1250 times and tapped volume was noted. . It is communicated in g/cc and is given by

$$Dt = m/Vi$$

Angle of Repose (θ):

This is the most extreme edge conceivable between the surface of a heap of powder or granules and the flat plane. The powders were permitted to move through the pipe settled to a remain at positive stature (h). The edge of rest was then ascertained by estimating the stature and sweep of the pile of granules framed.

$$\text{Tan } \theta = h/r \quad \theta = \tan^{-1}(h/r)$$

Compressibility Index:

The flowability of powder can be evaluated by comparing the bulk density (Db) and tapped density (Dt) of powder and the rate at which it packed down**.** Compressibility index is calculated by:

$$\text{Compressibility index (\%)} = Dt - Db/Dt \times 100$$

Hausner's Ratio:

It is the proportion of tapped density to the bulk density. It is given by:

$$\text{Hausner's ratio} = Dt / Db$$

Method of Preparation of Isosorbide dinitrate Buccal tablets:

Preparation: Direct compression method has been employed to prepare buccal tablets of Isosorbide dinitrate using various polymers.

Procedure: All the ingredients including drug, polymer and excipients were weighed accurately. The drug is thoroughly mixed with diluent on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend of each formulation was then compressed using a multi station tablet punching machine.

Table.1 Composition of Buccal tablets of Isosorbide dinitrate

Ingredients (mg)	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Isosorbide dinitrate	5	5	5	5	5	5	5	5	5	5	5	5
Guar gum	15	30	45	--	--	--	--	--	--	--	--	--
Carbopol 940	--	--	--	15	30	45	--	--	--	--	--	--
Xanthan Gum	--	--	--	--	--	--	15	30	45	--	--	--
Pectin	--	--	--	--	--	--	--	--	--	15	30	45
PVP K30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Mannitol	15	15	15	15	15	15	15	15	15	15	15	15
Lactose	105.5	90.5	75.5	105.5	90.5	75.5	105.5	90.5	75.5	105.5	90.5	75.5
Mg stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total	150	150	150	150	150	150	150	150	150	150	150	150

Post compression parameters of Buccal tablets of Isosorbide dinitrate:

Hardness test:

The crushing strength (kg/cm2) of tablets was determined by using monsanto hardness tester.

Friability test:

This was determined by weighing 10 tablets after dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated (% loss in weight).

Uniformity Weight:

The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation from the mean.

Uniformity of drug content:

Five tablets were powdered in a glass mortar and the powder equivalent to 10 mg of drug is placed in a stoppered 100 ml conical flask. The drug is extracted with 25 ml water with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 2 h and filtered into 50 ml volumetric flask through Whatman No.1 filter paper (Mean pore diameter 1.5 µm) and more solvent is passed through the filter to produce 50 ml. Aliquots of the solution are filtered through 0.22 µm membrane filter disc (Millipore corporation) and analyzed for drug content by measuring the absorbance at 405 nm wavelength against solvent blank.

Surface pH study:

The surface pH of the buccal tablets is determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.8 ± 0.05) for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min.

Swelling Index:

The swelling rate of the buccal tablet is evaluated by using of pH 6.8 phosphate buffer. The initial weight of the tablet is determined (w1). The tablets is placed in pH 6.8 phosphate buffer (6 ml) in a petridish placed in an incubator at 37 ± 1o C and tablet is removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h), blotted with filter paper and reweighed (w2).

The swelling index is calculated by the formula:

$$\textbf{Swelling index} = 100\,(w2-w1) / w1.$$

Mucoadhesion strength:

A modified balance method was used for determining the mucoadhesion strength. Fresh sheep buccal mucosa was obtained from the local slaughter house and used within 2 h of slaughter. The buccal mucosa was separated by removing the under lying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8. The fresh buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was attached to flat end of beaker with the help of cyanoacrylate gum, a watch glass attached to thin chains at equal distance froms the left hand pan. To the lower side of the watch glass the tablet was adhered just above the mucosa. The right pan consists of empty beaker, both the pans are balanced by adding suitable weights, then a 5 gm weight is removed from right hand pan, which lowered the left hand pan making tablet to come in contact with buccal mucosa. The balance was allowed in this position for 3 min. Then water was gradually added to the right hand pan until tablet detaches from the buccal mucosa. The weight required to detach the tablet from the mucosal surface gave the measure of mucoadhesive strength. Experiments were carried out triplicate and the averages of them are noted down.

In vitro drug release study :

The prepared buccal tablets were subjected to in vitro dissolution. Dissolution test was carried out using USP type 2 paddle method [apparatus 2]. The stirring rate was 50 RPM, pH 6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±0.5oC. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replace with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Isosorbide dinitrate at 405 nm by using UV-visible spectrophotometer.

RELEASE KINETICS:

In the present study, data of the in vitro release were fitted to different equations and kinetic models to explain the release kinetics of Isosorbide dinitrate from the buccal tablets. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

Kinetic Studies: Mathematical models:

Different release kinetic equations (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r2) was calculated.

Zero-order model:
Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation

$$Qt = Q0 + K0t$$

First Order Model:
The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

$$Log\ C = Log\ Co - kt/2.303$$

Higuchi model:
The first example of a mathematical model aimed to describe drug release from a system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then sustained to different geometrics and porous systems. This model is based on the hypothesis that Initial drug concentration in the is much higher than drug solubility;

$$Q = KH - t1/2$$

Korsmeyer-Peppas model:
Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model,

$$Mt / M\infty = Ktn$$

RESULTS AND DISCUSSION

Solubility: It was determined as per standard procedure

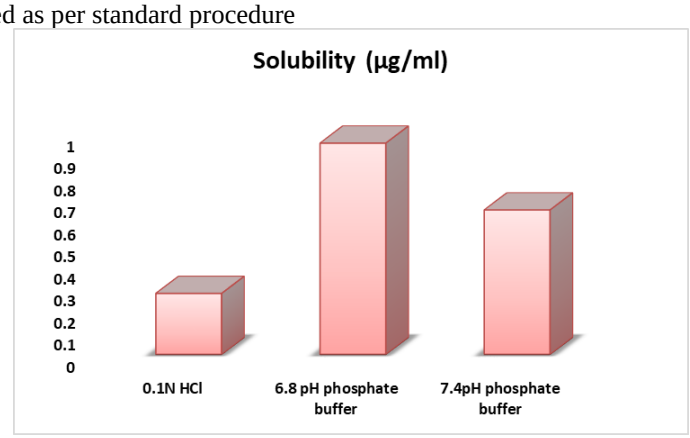

Figure.1 Graphical Representation of Isosorbide dinitrate solubility studies

Discussion: Isosorbide dinitrate was found to be more soluble in 6.8 pH phosphate buffer than other buffers like 7.4 pH buffer and 0.1N HCl Buffer.

Drug-Excipient compatibility studies:

FTIR of Pure Drug

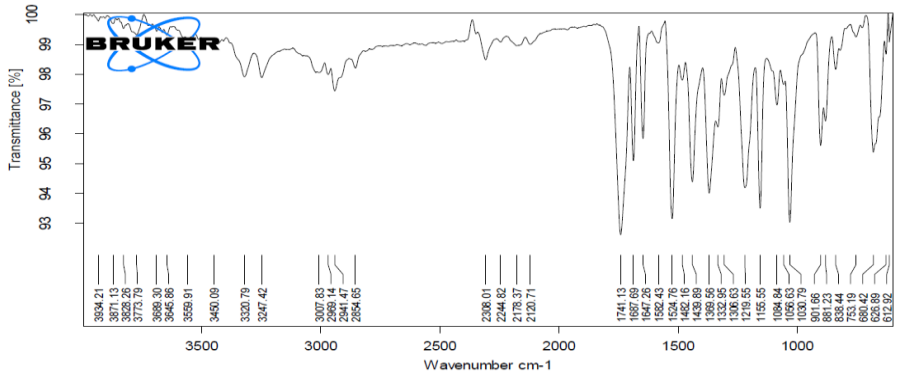

Figure.2 FTIR spectra of Isosorbide dinitrate

FTIR of Optimized formulation

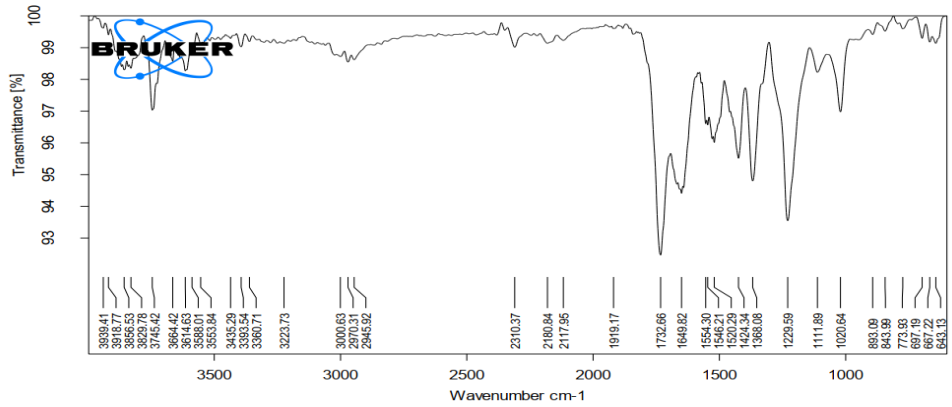

Figure.3 FTIR spectra of Isosorbide dinitrate + Excipients

Discussion: The IR spectrum of pure drug was found to be similar to the standard spectrum of Isosorbide dinitrate. From the spectra of Isosorbide dinitrate, combination of Isosorbide dinitrate with polymers, it was observed that all characteristic peaks of Isosorbide dinitrate were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and excipients.

UV Spectrum:

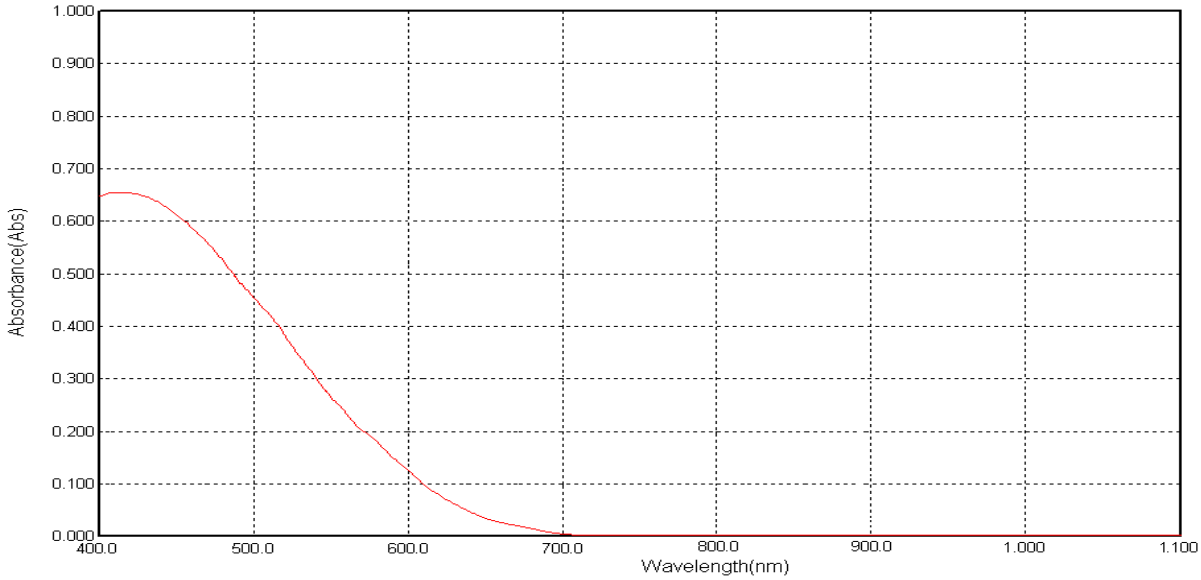

Figure.4 UV spectrum of Isosorbide dinitrate in 6.8 pH phosphate buffer

Discussion: The λ-max of at isosorbide dinitrate of 100% solution i.e 8 ppm (µg/ml) by using Single Beam Spectrophotometer (YIS-294) was found to be at 405.0 nm by using pH 6.8 phosphate buffer.

Standard Calibration Curve in 6.8 pH phosphate buffer:

Standard graph of Isosorbide dinitrate in pH 6.8 phosphate buffer shows linearity in the concentration range of 2-12 µg/ml with correlation coefficient of 0.999.

Table.2 Data for calibration curve of Isosorbide dinitrate in pH 6.8 phosphate buffer at 405 nm

Concentration (µg/ml)	Absorbance
0	0
2	0.179
4	0.328
6	0.495
8	0.654
10	0.795
12	0.946

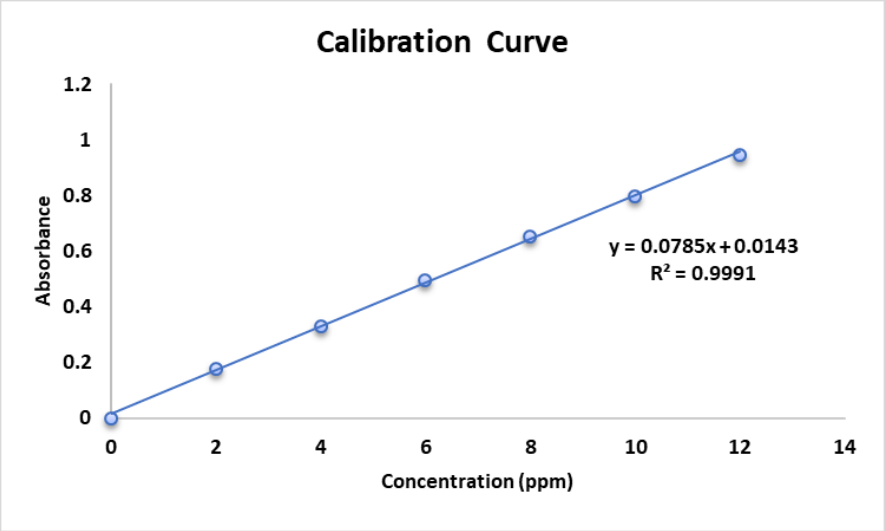

Figure.5 Standard Calibration Curve of Isosorbide dinitrate in pH 6.8 phosphate buffer at 405 nm

Discussion:

The linearity was found to be in the range of 2-12 µg/ml buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

Flow properties of powder blend :

Table.3 Flow properties of powder blend

Code	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index. (%)	Hausner's ratio
F1	28º18±1.85	0.312±0.002	0.432±0.002	18.94±1.20	1.19±0.01
F2	26º37±1.42	0.329±0.001	0.445±0.001	17.82±1.45	1.17±0.01
F3	25º45±1.16	0.338±0.003	0.450±0.003	16.57±1.61	1.16±0.02
F4	26º25±1.17	0.345±0.002	0.459±0.002	15.56±1.75	1.15±0.01
F5	28º19±1.34	0.327±0.002	0.439±0.003	17.87±1.85	1.18±0.02
F6	27º85±1.42	0.361±0.001	0.448±0.001	16.28±1.69	1.17±0.01
F7	29º69±1.10	0.337±0.003	0.452±0.002	15.62±1.24	1.16±0.02
F8	26º12±1.19	0.351±0.002	0.468±0.002	14.99±1.46	1.14±0.03
F9	28º37±1.02	0.320±0.003	0.445±0.001	16.71±1.20	1.17±0.02
F10	27º42±1.15	0.342±0.002	0.462±0.002	14.83±1.54	1.15±0.01
F11	25º08±1.37	0.357±0.002	0.475±0.002	12.59±1.36	1.12±0.02
F12	24º12±1.45	0.367±0.001	0.486±0.003	11.84±1.75	1.11±0.01

Discussion:

- The angle of repose of all formulations of immediate release mini tablets was done by funnel and cone method. The angle of repose found at 24º12±1.45– 29º69±1.10. This results indicates powder blends showed excellent flow property.
- The bulk density and tapped density of all formulations of immediate release mini tablets was measured by measuring cylinder. The bulk density found within 0.312±0.002-0.367±0.001g/cm^3.The tapped density found at 0.432±0.002-0.486±0.003g/cm^3.Both results are within acceptable limits.
- The Compressibility index of all formulations of immediate release mini tablet s range found at 11.84±1.75-18.94±1.20, it shows that good flow property.
- The Hausners ratio of all formulations of buccal tablets found at 1.11±0.01-1.19±0.01, which indicates that powder blend shows good flow property.

Post compression parameters of Isosorbide dinitrate buccal tablets:

Table.4 Hardness, Thickness, weight variation, friability, and drug content of Isosorbide dinitrate buccal tablets

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Weight uniformity	Friability (%)	% Drug content
F1	4.37±1.10	3.15±1.23	149.12±1.15	0.74±0.01	92.17±1.84
F2	5.49±1.24	3.32±1.37	150.37±1.33	0.65±0.02	94.15±1.20
F3	5.62±1.53	3.42±1.64	148.45±1.20	0.85±0.03	96.22±1.15
F4	4.12±1.25	3.37±1.26	149.18±1.46	0.80±0.01	94.84±1.30
F5	4.45±1.48	3.45±1.19	151.43±1.27	0.73±0.02	96.45±1.42
F6	5.61±1.67	3.61±1.61	150.51±1.48	0.62±0.03	98.20±1.15
F7	4.55±1.20	3.53±1.37	151.35±1.32	0.79±0.02	95.15±1.05
F8	5.12±1.36	3.61±1.20	148.45±1.45	0.65±0.01	96.36±1.12
F9	5.89±1.46	3.70±1.42	149.20±1.12	0.80±0.01	97.75±1.37
F10	5.51±1.12	3.68±1.31	151.34±1.39	0.76±0.02	97.25±1.45
F11	5.92±1.29	3.79±1.67	149.46±1.18	0.61±0.01	98.19±1.20
F12	6.36±1.37	3.82±1.46	150.51±1.27	0.51±0.02	99.42±1.14

Discussion:

- **Physical Parameters (Hardness & Friability)**
  The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 4.12±1.25 to 6.36±1.37 Kg/cm2. It was within the range of monograph specification. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.
- **Weight Variation**
  Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations ten tablets were randomly selected and weighed. The average weight of the Isosorbide dinitrate tablets were found in between were found to be within the 148.12±1.52-151.43±1.27 prescribed official limits (IP).
- **Percentage Drug Content**
  The drug content estimations showed the values in the range of 92.17±1.84% to 99.42±1.14% which reflects good uniformity in drug content among the formulations F1 to F12 and indicates these values were within specified range as per USP.

Table.5 Surface pH, Swelling Index, Mucoadhesive strength of Isosorbide dinitrate buccal tablets

Formulation code	Surface pH	Swelling Index After 8hours	Mucoadhesive strength (gm)
F1	6.5	25.10±1.15	19.45±1.14
F2	6.6	28.28±1.24	23.26±1.20
F3	6.8	32.37±1.37	27.44±1.16
F4	6.5	30.15±1.15	21.19±1.25
F5	6.8	34.42±1.20	26.32±1.17
F6	6.5	38.05±1.12	29.15±1.42
F7	6.4	33.20±1.25	23.38±1.20
F8	6.6	36.38±1.37	28.11±1.16
F9	6.7	39.12±1.16	31.20±1.51
F10	6.5	41.15±1.20	25.39±1.34
F11	6.7	45.24±1.21	28.45±1.42
F12	6.8	48.23±1.18	29.12±1.18

Discussion:

The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.4 to 6.8. Hence it is assumed that these formulations cause no any irritation in the oral cavity.

The swelling profile of different batches of the tablets is shown in Table. These profiles indicate the uptake of water into the tablet matrix, producing an increase in weight. The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface.

In formulations maximum swelling was seen with the formulation containing higher concentration of Pectin. Results indicate that as the concentration of polymers increases the swelling index increases.

The mucoadhesion of all the buccal tablets of varying ratios of polymers were tested and weight required to pull off the formulation from the mucous tissue is recorded as mucoadhesion strength in grams and results are given in. The mucoadhesivity of buccal tablets was found to be maximum in case of formulation F12 i.e. 45mg of Pectin.

***In vitro* dissolution of Isosorbide dinitrate buccal tablets F1 to F12**

Table.6 *In vitro* dissolution data of formulations F1 to F6

Time(hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	17.48±1.21	16.48±1.48	24.42±1.25	40.52±1.45	46.63±1.29	15.31±1.47
1	29.37±1.39	24.49±1.73	36.31±1.12	57.16±1.24	52.32±1.20	29.86±1.25
2	41.64±1.48	36.25±1.10	51.81±1.37	75.02±1.20	68.82±1.47	41.95±1.65
3	58.35±1.26	49.82±1.37	64.15±1.54	86.32±1.62	79.21±1.20	53.93±1.85
4	82.85±1.75	71.87±1.19	75.42±1.10	98.68±1.48	88.25±1.34	66.61±1.20
5	98.34±1.69	84.62±1.52	87.09±1.28		98.22±1.74	78.92±1.69
6		98.45±1.42	99.67±1.45			87.04±1.74
7						98.42±1.26
8						

Table.7 *In vitro* dissolution data of formulations F7 to F12

Time(hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
0.5	21.45±1.14	17.35±1.74	15.20±1.21	37.45±1.46	20.06±1.27	11.45±1.12
1	45.67±1.25	31.48±1.52	30.48±1.85	48.16±1.25	39.48±1.45	29.47±1.37
2	59.06±1.87	55.27±1.61	44.61±1.15	53.20±1.15	51.02±1.62	35.59±1.45
3	63.15±1.51	68.18±1.28	59.42±1.25	61.78±1.48	56.45±1.45	48.56±1.85
4	75.65±1.28	73.09±1.45	65.20±1.61	79.45±1.35	65.67±1.20	56.67±1.14
5	88.49±1.12	82.32±1.62	73.51±1.45	88.10±1.82	79.28±1.59	70.45±1.29
6	99.02±1.27	90.35±1.45	80.49±1.75	99.69±1.67	86.45±1.74	83.38±1.45
7		99.25±1.08	88.37±1.20		99.14±1.26	90.45±1.37
8			98.12±1.39			99.16±1.45

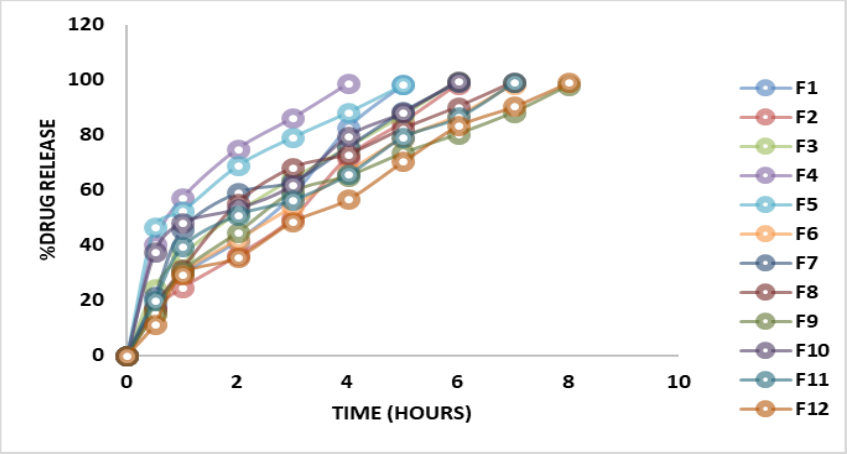

Figure.6 *In-vitro* drug release profiles of F1-F12

Discussion: Among all the 12 formulations F12 formulation is optimized, as it shows maximum drug release at the end of 8hrs, which suits the buccal drug delivery system criteria as per our studies. Further drug release kinetics were performed to F12 formulation.

Drug Release Kinetics:

ZERO ORDER:

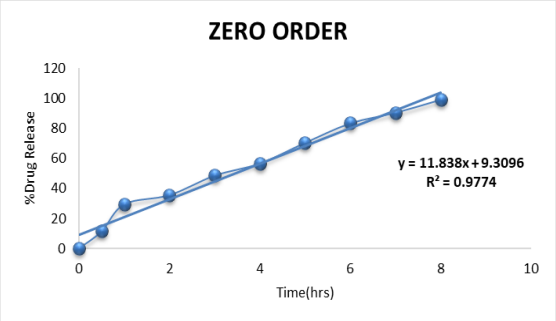

Figure.7 Zero order graph of F12 formulation

FIRST ORDER:

Figure.8 First order graph of F12 formulation

HIGUCHI PLOT:

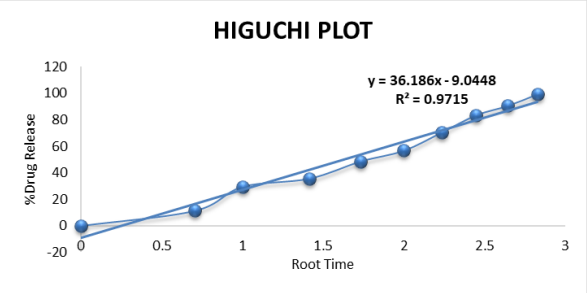

Figure.9 Higuchi plot of F12 formulation

PEPPAS PLOT:

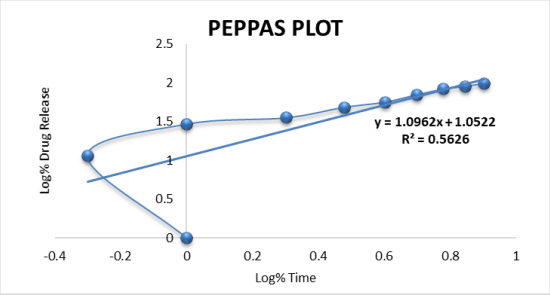

Figure.10 Peppas plot of F12 formulation

Table.8 Drug release kinetics:

	R^2 values				n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F12	0.977	0.784	0.971	0.562	1.096

Discussion: The in vitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows R2 value 0.977. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The 'n' value is 0.921 for the optimised formulation (F12) i.e., n value was n > 0.89 this indicates Super case II transport. The release kinetics for the optimized formula are shown in table**.**

CONCLUSION

Isosorbide dinitrate is an vasodilator medicine. The bioavailability of oral Isosorbide dinitrate is reduced due to extensive hepatic metabolism. Since buccal route by passes first-pass effect. Therefore, it is selected as suitable drug for the design of Buccal drug delivery system with a view of improve its oral bioavailability and patient compliance. In the present study, an attempt was made to prepare buccal tablets of Isosorbide dinitrate in order to overcome bioavailability problems, to reduce dose dependent side effects. Buccal tablets containing drug was prepared by direct compression method by using combinations of polymers (Guar gum, Carbopol 940, Xanthan Gum, Pectin). Estimation of Isosorbide dinitrate was carried out spectrophotometrically at 405 nm. The Buccal tablets were evaluated for physical parameters like appearance, hardness, thickness, weight variation, friability, swelling index, and surface pH; biological parameter-mucoadhesive strength; and other parameters such as drug content uniformity, in-vitro release, drug excipient interactions (FTIR) The Buccal tablets prepared by direct compression were found to be of uniform thickness and weight, smooth appearance with uniform drug content, good hardness and mucoadhesive strength. An increase in polymer concentration brought in an increase in mucoadhesive strength. The maximum mucoadhesive strength is shown by formulation F12 (45mg Pectin). FTIR spectroscopic studies indicated that there are no drug- excipients interactions. Among all the 12 formulations F12 formulation is optimized, as it shows maximum drug release at the end of 8hrs which suits the buccal drug delivery system criteria as per our studies. Optimized formulation (F12) displayed that it follows zero order release kinetics and drug release follows super case II transport mechanism.

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