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FORMULATION DEVELOPMENT AND EVALUTION OF METFORMIN SUBLINGUAL TABLETS

Shraddha Nagpure*

Deprtmen of Quality Assurance, SND College of Pharmacy, Yeola (Nasik) Pin-423401, Maharashtra, India.

***Corresponding Author: Shraddha Nagpure**
Deprtmen of Quality Assurance, SND College of Pharmacy, Yeola (Nasik) Pin-423401, Maharashtra, India.
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ABSTRACT

The aim of present work was to prepared and characterized Metformin Sublingual tablet by using superdisintegrants to increase the rate of Disintegration and Dissolution. Metformin sublingual tablet is prepared by using 3×3 factorial design. The Superdisintegrants like Cross povidon, Polyvinyl pyrrolidon and Microcrystalline cellulose were used in different concentration in each formulation which increase the bio-availability of formulation. All formulations were prepared by Direct compression method. The prepared F1 formulation is the found to be best formulation among all 9 formulations of improving solubility of drugs and prepared Metformin Sublingual tablets were evaluated for weight variation, thickness, hardness, drug content, disintegration and dissolution rate studies. The F1 formulation was found to be 8 sec of disintegration time and 12 min of dissolution time. The developed sublingual drug delivery of Metformin sublingual tablet was one of the alternative route of administration to improve bioavailability through sublingual mucosa and improve patient compliance.

KEYWORDS: Metformin sublingual tablet, Formulation, Evaluation.

NTRODUCTION

In some cases or in some medications rapid onset of action is required. Sublingual Drug delivery system is a comfortable route for rapid onset of action & It directly absorb in the Systemic circulation & gives faster Therapeutic action Dysphagia (Difficulty in swallowing) is associated with all age groups patients especially for elder, children, and patients who are mentally retarded, uncooper-ative, nauseated patient. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route. For these formulations, the small volume of saliva is usually suffi-cient to result in tablet disintegration in the oral cavity. Sublingual absorption is mostly rapid in action, but also short acting in duration.

Sublingual administration of the drug means placement of the drug under the tongue and the drug reaches directly into the circulation system through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained into systemic circulation. The routes of absorption via the highly vascularized buccal and sublingual mucosa allow the substance a more direct access to the blood circulation, thus providing direct systemic administration of drug.[1] It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method.[2]

Mechanism of sublingual absorption

The mucosal lining consists of three distinct layers. The outermost layer is the epithelial membrane, which consists of stratified squamous epithelial cells and it has a protective barrier function. The innermost layer of the epithelial membrane is called the basement membrane. Below the epithelium lies the lamina propria followed by the sub-mucosa. The lamina propria is a hydrated and less dense layer of connective tissue containing collagen and elastic fibres.[3] The oral sub-mucosa is richly supplied with blood vessels.[4] The absorption through the mucous membrane in the sublingual region, the drug instantly diffuses into venous blood. The venous blood from the sublingual region of the oral cavity drains into a common trunk, which then drains via the internal jugular vein, the sub clavian vein, and the brachiocephalic vein directly into the superior vena cava. Thus, venous return from these regions enter the systemic circulation, bypassing the pre-systemic drug elimination, unlike in oral administration. Direct drainage into systemic circulation results in the immediate systemic availability of the drug and rapid onset of action.[5]

Anatomy and physiology of mucosa:
The thickness of mucosa is 100-200 µm. Mucosa is composed of neutral but polar lipid e.g. cholesterol sulfate, glucosyl ceramide. The saliva is composed of 99.5 % water, proteins, glycoprotein, high potassium (7X Plasma), bicarbonate (3X plasma), calcium, phosphorous, chloride, low sodium (1/10X Plasma). The sublingual gland contain 5 % saliva. The pH of saliva is 5.6-7.0 9.

Factors affecting the sublingual absorption[6-7]

1. Thickness of oral epithelium: As the thickness of sublingual epithelium is 100-200 µm which is less as compared to buccal & sublingual thickness. So the absorption of drugs is faster due to the thinner epithelium and also the immersion of drug in smaller volume of saliva.
2. Lipophilicity of drug: For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
3. pH and pKa of the saliva: As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
4. Oil to water partition coefficient: Compounds with favorable oil to- water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.
5. Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous sublingual fluids i.e. biphasic solubility of the drug is necessary for absorption.
6. Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.

Advantages[8]

1. Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
2. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
3. Low dosage gives high efficacy as hepatic first-pass metabolism is avoided and also reduces the risk of side effects.
4. Due to rapidity in action, these sublingual dosage forms are widely used in emergency conditions e. g. asthma.
5. The large contact surface of the oral cavity contributes to fast or rapid and extensive drug absorption.
6. 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.
7. Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
8. They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Disadvantages[9]

1. Sublingual medication can't be used when a patient is uncooperative. Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
2. The patient should not smoke while taking sublingual medication because smoking causes vasoconstriction of the vessels. This will decrease the absorption of the medication.

Formulation aspects of sublingual tablet
The distinct feature in the formulation of sublingual tablets involves the selection of suitable excipients of bland taste that shall ultimately resulting in a rapidly disintegrating tablet their by enhancing the dissolution of active ingredient.[10]

Compressed sublingual tablets
Compressed sublingual tablets can be prepared by two different methods:

a) Wet Granulation method
b) Direct compression method

The directly compressible sublingual tablet formulation contains directly compressible soluble excipients, a super disintegrant, and lubricant. It may also contain microcrystalline cellulose, a dry binder, buffers, surface-active agents, sweeteners, and flavors. Sugar-based excipients are widely used as bulking agents because of their high aqueous solubility, sweetness, good taste-masking and pleasant feeling in the mouth. Nearly all sublingual formulations incorporate some saccharide-based material. The choice of a suitable disintegrants and its amount are critical for increasing disintegration and dissolution time.

MATERIALS AND METHODS

Metformin was obtained from Mylan Pharmaceutical ltd, Sinner, Nasik. Cross povidon, polyvinyl pyrrolidon, Micro crystalline cellulose, Hydroxy propyl methyl cellulose, Mannitol, Magnesium stearate are obtained from S.D. Fine chemicals, Mumbai.

Formulation Of Metformin Sublingual Tablet[10-12]
Metformin Sublingual tablet were prepared by using different super disintegrants like Cross povidon, polyvinyl pyrrolidon K30 and Micro crystalline cellulose with the method of direct compression. Binder like

hydroxy propyl methyl cellulose, Diluent like Mannitol, Lubricant like Magnesium stearate were used for preparation of Metformin Sublingual tablets. All nine formulation's composition was made by using 3×3 factorial design. All the ingredient except lubricant like magnesium stearate were uniformly blended, mixed and passes through #44 to get fine particles. Then finally magnesium stearate was added. Then mixed it very well. The resultant mixture of 100mg was compressed into tablets by using multi-tooling tablet compression machine. All the formulation F1-F9 containing 100 mg tablets were prepared.

Evaluation Of Metformine Tablets[13-18]

1. Weight variation Twenty tablets were randomly selected from each batch and individually weighted. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.
2. Thickness uniformity three tablets were selected randomly from each batch.

Evaluations

General appearance: The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as accounting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Wetting time: A piece of tissue paper (12 × 10.75 cm) folded twice was placed in a small petri dish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting of tablet was measured.

Uniformity of weight: I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight as per the IP.

Friability: It is the measure of mechanical strength of tablets. Roche friabilator can be used to determine the friability by following procedure. A pre-weighed tab-let was placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, drop-ping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 min. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

%Friability = loss in weight / Initial weight × 100. The percentage loss should be less than 1 %.

Tablet hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the Metformin tablet of each formulation was determined using Monsanto Hardness tester.

In-vitro dispersion time: In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of 0.1 N Hcl buffer pH 7. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed and measured.

In-vitro disintegration test: The test was carried out on 6 tablets using the apparatus specified in I.P. distilled water at 37ºC ± 2º C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured in seconds. Standard time required for Sublingual tablet is within 3 minutes as per IP.

Uniformity of drug content: The Metformin content in sublingual tablet was estimated as follows-

ASSAY

1. **Standard preparation**- Weigh accurately about 30mg standard Metformin IP. Add it in 100 ml volumetric flask. Dissolve the Metformin drug in the 0.1 N Hcl And mix well.
2. **Sample preparation**- For this 100mg Metformin tablet of each batch is taken which is equivalent to 30mg standard Metformin. Triturate it very well with the help of morter & pestle one by one then add it separately in 10ml volumetric flask. Make up the volume with 0.1 N Hcl & assayed individually.

Percent water absorption: The water uptake characteristics of the loose disintegration powder allows and evaluation of both the intrinsic swelling and the wettability of the super disintegrants water uptake and performed at room temperature. A piece of tissue paper folded twice and was placed in small petri dish containing 6 ml water. A tablet was put on the paper and time required for completing wetting as 0.52min. The wetted tablet was weighted. Water absorption ratio was determined using following equation.

% water absorption = (Wb- Wa/ Wb).100

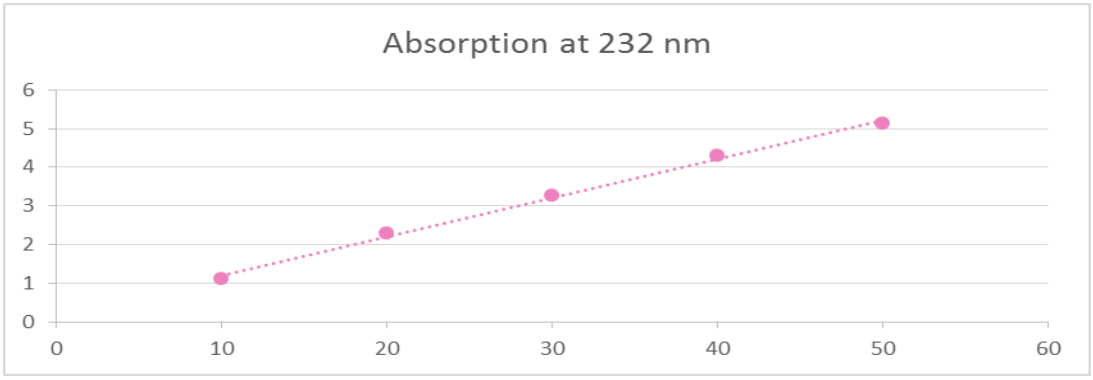
Where, Wb is the weight after water absorption, Wa is the weight before water absorption.

In-vitro release study: The in-vitro dissolution studies were performed using type II dissolution apparatus at 100 rpm. The dissolution medium containing of o.1 N HCl (900 ml), maintained at 37ºC ±2ºC. The solution (5 ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer at 234 nm for Metformin sublingual tablet. At each time of withdrawal, 5 ml of fresh corresponding dissolution medium was replaced into the dissolution flask. It was made clear that none of the ingredients used in the sublingual formulations interfered with the assay. The release studies were conducted in triplicate. The parameters of dissolution studies are given followings.

USP dissolution apparatus……. Type II (Paddle)

Table 1: Formulation Table of Sublingual Tablets of Metformin (F1 to F9).

Sr. No.	Drug/Excipient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	**Metformin**	30	30	30	30	30	30	30	30	30
2.	**Cross-Povidon**	3	3	3	3	3	3	3	3	3
3.	**PVP 30**	2	4	8	2	4	8	2	4	8
4.	**Micro-crystalline cellulose**	4	6	8	4	6	8	4	6	8
5.	**Hydroxy propyl methyl cellulose**	6	6	6	6	6	6	6	6	6
6.	**Mg-stearate**	2	2	2	2	2	2	2	2	2
7.	**Mannitol**	53	49	43	49	49	43	53	49	43
8.	**Tablet total weight**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**



Graph 1: Ultra sound absorption studies.

RESULT AND DISCUSSION

In the current study, Metformin sublingual tablet has been made by using direct compression method. Pre-compression parameters are performed for these tablets such as Bulk density, Tapped density, Carr's index, Hausner's ratio and angle of repose and for post compression parameters are also performed such as Weigh variation, Hardness, Dug content uniformity, Wetting time, water absorption ratio, Disintegration time and in-vitro dissolution studies.

Evaluation Parameters

Precompression Parameters of Blends

The bulk density of pre-compression blends of Metformin was found to be in the range of 0.620 to 0.644 g/ml, Tapped density in the range of 0.670 to 0.696 g/ml, Carr's index values were in the range of 5.1% to 9.4%. Housner's ratio in the range of 1.047 to 1.101 and Angle of repose between 31.50° to 40.40°. All the values were found to be within the prescribed limits according to the IP, thus ensuring good flow.

Post Compression Parameters

Thickness, Hardness and Friability

The hardness of the Metformin sublingual tablet formulation was found to be in the range of 2.2 to 3.4 kg/cm2. Thickness values were found to be in the range of 3.07 to 3.36 mm and friability values were found to be in the range of 0.53% to 0.83% which was found to be according to the I.P. limits and thus ensuring good mechanical strength to all the tablet formulations.

Uniformity of weight

All the prepared sublingual tablets of Metformin were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed I.P. limits.

Uniformity of drug content

The values indicates uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 97.96% to 99.43%.

Disintegration time

The percent water absorption was found to be in the range of 41.57% to 53.92% which is in the I.P limits.

Among the tablets prepared F1 formulation was found to be promising and has shown low disintegration time 8 sec.

In vitro dissolution study

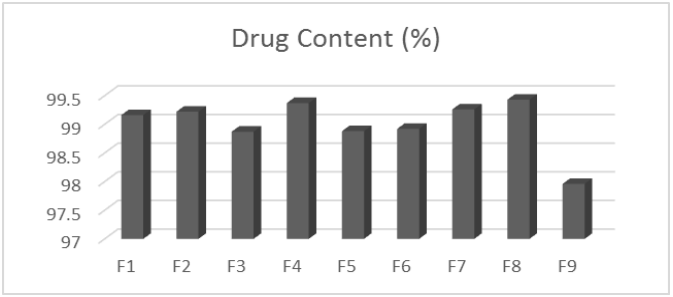
In vitro dissolution studies were performed in 0.1 N Hcl buffer maintained at a temperature of 37°c at RPM of 100 in a USP II apparatus the absorbance's noted at 234 nm. The dissolution results showed gradient increases with the the increase in the concentration of the super disintegrants. Among all the formulation F1 was found to show best results with 98.98% release within 12 mins.

Table 2: Pre-Evaluaton Parameters Of Powder Blend.

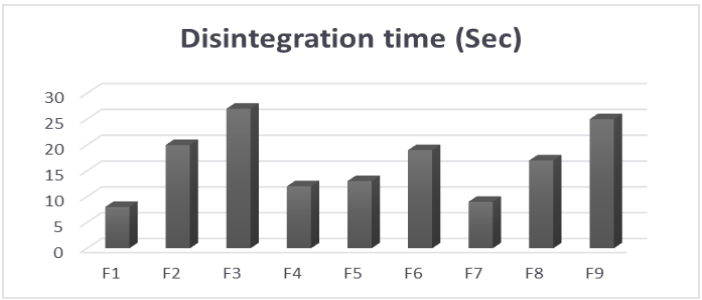
Formulation code	Bulk Density (gram/ml)	Tapped Density (gram/ml)	Carr's Index (%)	Hausner's Ratio	Angle of repose (°)
F1	0.641 ± 0.0052	0.680 ± 0.006	5.7 ± 0.406	1.060 ± 0.02	37.2 ± 0.29
F2	0.628 ± 0.003	0.676 ± 0.013	7.1 ± 0.343	1.076 ± 0.004	40.05 ± 0.53
F3	0.620 ± 0.023	0.680 ± 0.005	8.8 ± 0.242	1.097 ± 0.003	34.19 ± 0.2
F4	0.632 ± 0.001	0.694 ± 0.002	8.9 ± 0.308	1.098 ± 0.005	31.50 ± 0.2
F5	0.640 ± 0.003	0.674 ± 0.004	5.1 ± 0.290	1.053 ± 0.01	32.94 ± 0.38
F6	0.64 ± 0.0023	0.670 ± 0.006	4.5 ± 0.326	1.047 ± 0.003	33.43 ± 0.27
F7	0.632 ± 0.0012	0.684 ± 0.006	7.6 ± 0. 249	1.082 ± 0.003	40.40 ± 0.43
F8	0.644 ± 0.006	0.690 ± 0.002	6.7 ± 0. 142	1.071 ± 0.01	32.37 ± 0.28
F9	0.630 ± 0.004	0.696 ± 0.005	9.4 ± 0.51	1.101 ± 0.003	35.02 ± 0.22

Table 3: Post Parameters of Metformin Sublingual Tablet.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation	% Drug Content	Disintegration Time (Sec)
F1	3.36 ± 0.013	2.2 ± 0.192	0.68 ± 0.02	1.983 ± 0.006	99.16	8
F2	3.12 ± 0.014	2.4 ± 0.163	0.62 ± 0.01	1.933 ± 0.002	99.22	20
F3	3.30 ± 0.02	2.6 ± 0.125	0.72 ± 0.03	1.972 ± 0.004	98.87	27
F4	3.07 ± 0.043	3.4 ± 0.127	0.53 ± 0.11	1.851 ± 0.004	99.37	12
F5	3.22 ± 0.058	3.2 ± 0.158	0.64 ± 0.07	2.019 ± 0.019	98.88	13
F6	3.18 ± 0.053	3.2 ± 0.089	0.70 ± 0.04	1.943 ± 0.11	98.92	19
F7	3.16 ± 0.076	2.8 ± 0.130	0.68 ± 0.02	1.896 ± 0.01	99.26	9
F8	3.10 ± 0.025	2.4 ± 0.098	0.66 ± 0.02	1.896 ± 0.02	99.43	17
F9	3.26 ± 0.026	2.2 ± 0.167	0.83 ± 0.03	1.968 ± 0.002	97.96	25



Graph 2: Drug Content (%) Of Metformin Sublingual Tablet



Graph 3: Disintegration Time Of Metformin Sublingual Tablets

Table 4: Comparative Dissolution Data Of Metformin Sublingual Tablet.

Formulation code/ Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
4	39.27%	22.02%	13.55%	25.30%	21.21%	16.23%	27.37%	20.14%	13.17%
8	71.38%	38.06%	28.21%	51.09%	39.81%	32.82%	52.34%	34.28%	26.07%
12	98.07%	59.01%	38.61%	74.24%	59.27%	51.07%	77.64%	49.03%	39.26%
16	-	77.76%	50.01%	93.51%	78.8%	67%	99.98%	62.88%	51%
20	-	91.38%	62.33%	-	99.86%	83.03%	-	86.19%	63.09%
24	-	-	77.08%	-	-	98.97%	-	97.68%	76.01%
28	-	-	89.27%	-	-	-	-	-	89.21%

CONCLUSION

Sublingual tablet of Metformin were prepared by using direct compression method. The concept of formulating sublingual tablets containing metformin offers faster disintegration & dissolution characteristics with increased bio-availability. F1 formulation consist - Metformin (30mg), Cross Povidon (3mg), Polyvinyl Pyrralidon (2mg), Micro crystalline cellulose (4mg), Hydroxy propyl methyl cellulose (6mg), Magnesium stearate (2mg), Mannitol (quantity required to fulfil 100mg) were selected. Various physiochemical parameters were evaluated for this F1 formulation shown good results. It conclude that development of sublingual drug delivery of metformin tablets was one of the alternative route of administration to avoid first pass effect & to improve the bio-availability of metformin through sublingual mucosa. It improve patient compliance also.

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