AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Sublingual Tablets of Amlodipine Besylate Containing Beta-Cyclodextrin

Vankani Ankit K[1]*

1.Department of Pharmaceutics, Babaria Institute of Pharmacy, Vadodara - Mumbai, National Highway 8, Varnama, Gujarat 391240

ABSTRACT

Amlodipine Besylate is a molecule used in Hypertension and currently available in tablet dosage form. The objective of present study was to develop and evaluate Amlodipine Besylate intraoral sublingual formulation for faster release and absorption. Four formulations containing varying concentrations of Croscarmellose sodium and β-Cyclodextrin were formulated. Various evaluations like weight variation, % friability, Hardness, diameter, water absorption ratio, wetting time, disintegration time, drug content and calibration curve were performed. From the results, it was concluded that all batches pass the evaluation tests with F4 showing the fastest wetting and Disintegration. From the data of Dissolution studies it was concluded that formulation F4 showed highest drug release in 10 minutes. It can be concluded that sublingual tablets of Amlodipine Besylate will prove to be patient friendly.

Keywords: Amlodipine Besylate, Croscarmellose sodium, β-Cyclodextrin, sublingual

*Corresponding Author Email: ankitkv.2712@gmail.com
Received 21 July 2014, Accepted 31 July 2014

Please cite this article as: Vankani AK *et al.*, Formulation and Evaluation of Sublingual Tablets of Amlodipine Besylate Containing Beta-Cyclodextrin. American Journal of PharmTech Research 2014.

INTRODUCTION

Since Decades, oral drug administration has been established as one of the most convenient and widely accepted routes for the delivery of large number of the therapeutic drugs. Traditionally, oral formulations include tablets, capsules and liquid dosage forms administered orally, swallowed and travelling the Gastrointestinal Tract for post intraoral absorption.[1] Swallowing of conventional tablets and capsules is a common problem amongst patients of all age groups, especially paediatrics, geriatrics, cardiac, dysphagic and diabetic patients.

One study has shown that out of 1576 patients, 26% patients experienced difficulty in swallowing tablets because of large size, surface, shape and taste.[2] Apart from problems related to swallowing, Gastrointestinal Tract has some undesirable physiological properties like degradation of Drug molecule by gastric acidic pH, degradation due to digestive enzymes, first pass metabolism and elimination, irritation by drug molecule to the intestinal tract, GIT transit time, poor absorption, etc. limits the administration of some drug molecules especially proteins, peptides and polypeptides through the GI Route.[1, 3]

The search for alternative modes for drug delivery has led to exploration of the various intraoral mucosae as possible routes of drug administration. [(4)] For the last few decades, researchers are trying to develop intraoral delivery systems (IDS) which will lead to desirable exposure of Drug to Mucosal Surface for optimum therapeutic action. As a result, unconventional Oral Dosage forms are being developed with importance on pregastric absorption by different tissues of the oral cavity to avoid first pass and gut wall metabolism, to raise the bioavailability or ameliorate convenience of dosing. [(2)]

Sublingual tablets are to be placed under the tongue and to produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue.

Figure 1 Administration of Sublingual tablet[7]

Suitability of API for preparation of sublingual tablet: [7, 8]

Many drug properties could potentially affect the performance of sublingual tablets: The solubility, Crystal morphology, Particle size, Hygroscopicity, Compressibility, and Bulk density of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration.

Fast-disintegrating sublingual tablets:[7-11]

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.

Bioadhesive sublingual tablet: [7-11]

The new sublingual tablet concept presented is based on interactive mixtures consisting of a water-soluble carrier covered with fine drug particles and a bioadhesive component. With this approach, it is possible to obtain rapid dissolution in combination with bioadhesive retention of the drug in the oral cavity.

Bioadhesion is usually defined as the bond formed between two biological surfaces or between a biological and a synthetic surface. The term mucoadhesion is used when the mucus or mucosal surface is involved in these adhesive bonds.

Thin film drug delivery:[7-11]

The sublingual delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament. Thin film is more stable, durable and quicker dissolving than other conventional dosage forms.

Lipid matrix sublingual tablet: [7-11]

Lipid Matrix Sublingual Tablet is formulated using advances in sublingual and liposomal technology to create a dosage form that offers a faster and more complete absorption than traditional oral routes of administration. The Lipid Matrix Sublingual Tablet is a bioavailable, quick, convenient, and consistent dosage form for many specialty nutraceuticals that are often taken orally. Examples Include: Glutathione MB12 (Methylcobalamin), Melatonin

Advantages of sublingual formulation: [12-14]

Administration and termination of therapy is easy. This route can administer drugs that are unstable in the acidic environment of the stomach or are destroyed at the enzymatic or alkaline environment of the intestine. It permits localization of the drug to the oral cavity for prolonged period of time. It offers an excellent route for systemic delivery of drugs having drawbacks of first pass metabolism, convenient for drugs that show poor bioavailability. Significant dose reduction can be achieved.

Disadvantages: [12-14]

Drugs which irritate the mucosa or have bitter or unpleasant taste or an obnoxious odour or unstable at buccal pH cannot be administered by this route. Only drugs with small dose requirements and drugs that are absorbed by passive diffusion can be administered by this route. Eating and drinking may become restricted.

Market Preparation:

1. Tenormin sublingual tablet (Isoproterenol)
2. Microtab sublingual tablet (Nicotine)
3. Nascobal sublingual tablet (Vitamin B_{12})
4. Subuter sublingual tablet (Buprenorphine)
5. Nitroquick sublingual tablet (Nitroglycerin)

MATERIALS AND METHOD:

Amlodipine Besylate, Mannitol, Povidone K30, Saccharin sodium, Croscarmellose sodium (CCS), Talc, Magnesium stearate, Menthol, β-Cyclodextrin

Formulation of Sublingual Tablets

Sublingual Tablets were compressed by Direct Compression Method. Weigh all the ingredients accurately and pass through sieve# 40. Mix all the ingredients geometrically except Talc and Magnesium Stearate. Then lubricate the blend with Talc and Magnesium Stearate. Compress the powder mixture in the Tablet compression machine with suitable punch set. Evaluate the tablets for different tests.

Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material. As Amlodipine Besylate is having unacceptable taste, addition of β-Cyclodextrin proves to be beneficial in taste masking. β-Cyclodextrin is the most commonly used Cyclodextrin, although it is the least soluble. It is the least expensive Cyclodextrin; is commercially available from a number of sources; and is able to form inclusion complexes with a number of molecules of pharmaceutical interest. In oral tablet formulations, β-Cyclodextrin may be used in both wet-granulation and direct-compression processes. The physical properties of β-Cyclodextrin vary depending on the manufacturer. However, β-Cyclodextrin tends to possess poor flow properties and requires a lubricant, such as 0.1% w/w magnesium stearate, when it is directly compressed[17, 18]

Table 1 Formulation Compositions

Ingredients	**F1** **Qty/ tablet (mg)**	**F2** **Qty/ tablet (mg)**	**F3** **Qty/ tablet (mg)**	**F4** **Qty/ tablet (mg)**
Amlodipine Besylate	5.0	5.0	5.0	5.0
Mannitol	71.0	51.0	71.0	51.0
β-Cyclodextrin	20.0	40.0	20.0	40.0
Povidone K30	5.5	5.5	5.5	5.5
Croscarmellose sodium	1.5	1.5	3.5	3.5
Talc	1.5	1.5	1.5	1.5
Magnesium Stearate	2.0	2.0	2.0	2.0
Menthol	1.5	1.5	1.5	1.5
Total	**110.0**	**110.0**	**110.0**	**110.0**

Evaluation Parameters: [15, 16]

Weight variation test:

To study weight variation, 20 tablets were weighed using an electronic balance and the test was performed according to the official method.

Table 2 Standard Weight Variation Limits

Average Weight of Tablet (mg)	**Maximum % Difference Allowed**
80 or less	10
80-250	7.5
More than 250	5

Friability:

Friability is evaluated from percentage weight loss of 6.4gm or 20 tablets tumbled in a friabilator at 25 rpm for 4 min. The tablets then are de-dusted, and the loss in weight caused by fracture or abrasion was recorded as percentage weight loss.

Tablet having **friability below 1%** is considered as acceptable limit for friability test. Friability is calculated as following formula:

% Friability= Initial weight – Final weight/Initial weight * 100

Hardness:

Tablet requires certain amount of hardness to withstand mechanical shock. Tablet hardness has been defined as "the force required to break a tablet in a diametric compression test." The Monsanto tester was used to measure tablet hardness.

Thickness:

Thickness is measured by sliding caliper scale (Vernier calipers). Tablet thickness should be controlled within 5% variation of a standard value.

Diameter:

Thickness is measured by sliding caliper scale (Vernier calipers). Tablet thickness should be controlled within 5% variation of a standard value.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet is then weighed. It can be calculated by following formula:

Water absorption ratio= Wa – Wb/Wa * 100

Where,

Wa= Weight of tablet after water absorption

Wb= Weight of tablet before water absorption

Wetting time:

A piece of tissue paper (12 cm * 10.75 cm) folded twice was placed in a Petri dish containing 9 ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting is noted.

Disintegration time

Disintegration of Tablets was performed using DT Apparatus. Time required for disintegration of tablet was noted.

Standard calibration curve of Amlodipine Besylate

Weigh 100 mg of drug and dissolve in 5 ml methanol and sonicate for 10 min. Make up the volume up to 100 ml with phosphate buffer pH 7.4. Filter the above solution. Pipette out 10 ml from the above solution and dilute into 100 ml volumetric flask. From the above solution, pipette out 0.5, 1, 2, 3, 4, 5 ml of solution and dilute to 10 ml with same phosphate buffer. Measure the absorbance at 239 nm against blank.

Drug content:

Dissolve the triturated powder of average weight of tablet in 5 ml methanol and dilute into 100 ml volumetric flask with phosphate buffer pH 7.4. Filter the above solution and measure the absorbance at 239 nm against blank.

Dissolution study

Perform *in-vitro* dissolution studies using USP dissolution apparatus type II at 75 rpm. Dissolution test carry out using 900 ml of 7.4 pH phosphate buffer, at 37 ± 0.5^{o}C. A 5 ml sample of solution is withdrawn from the dissolution apparatus and the samples are replaced by fresh dissolution medium then the samples are filtered and absorbance are measured at 239 nm using UV/Visible spectrophotometer.

Dissolution test:

- No. of test samples= 6 tablets
- Phosphate buffer pH=7.4 (900 ml).
- USP Apparatus – Paddle at 75 rpm.
- Temperature- 37±0.5° C
- 5 ml sample withdraw, filter and dilute and analyze by UV at 239 nm.

Plot the graph of cumulative % drug release vs time and % drug release vs time.

RESULTS AND DISCUSSION:

Following results were obtained from the various evaluations that were performed for formulations F1 to F4.

Table 3 Evaluation of Sublingual Tablets

Parameter	F1	F2	F3	F4
Weight Variation (%)	109.0 ± 2.51	111.0 ± 4.63	108.0 ± 3.09	109.5 ± 2.82
% Friability	0.76	0.61	0.47	0.55
Hardness (Kg/cm^2)	3.5	3.0	3.0	3.0
Diameter (mm)	5.89 ± 0.026	6.01 ± 0.035	5.93 ± 0.054	5.96 ± 0.081
Water Absorption Ratio (%)	2.6	13.28	17.55	21.22
Wetting Time (seconds)	48	68	36	29
Disintegration Time (seconds)	61	75	49	34
Drug Content (%)	97.14	98.42	95.27	96.65

Dissolution Studies:

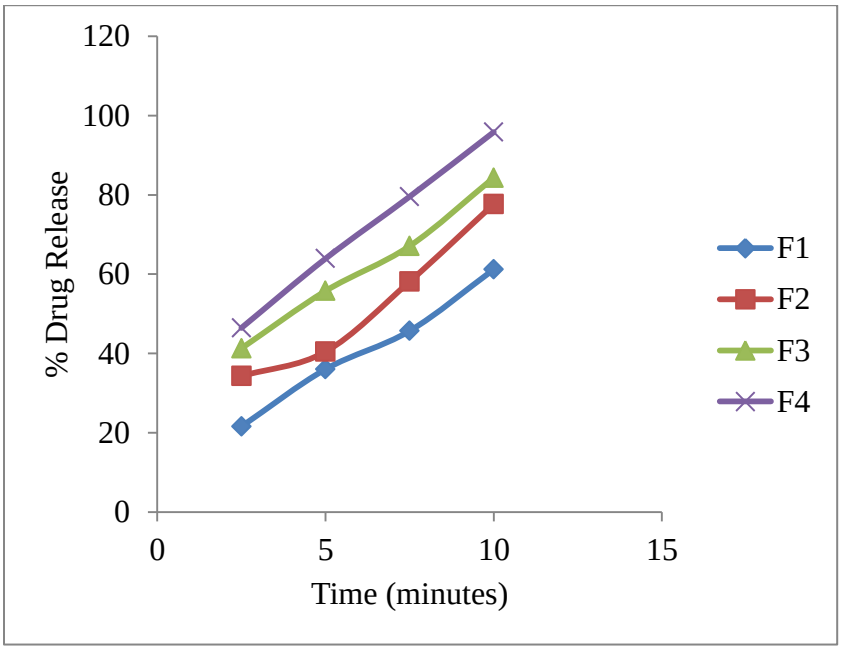

Figure 2 Graph of Dissolution Studies of Formulations

Table 4 Dissolution Studies of formulations

Time (minutes)	F1	F2	F3	F4
2.5	21.56	34.28	41.27	50.42
5	38.01	40.43	55.75	63.91
7.5	45.67	58.12	67.08	79.55
10	61.19	77.68	84.32	95.83

CONCLUSION:

In the present study, Sublingual tablets of Amlodipine Besylate were prepared using Croscarmellose Sodium and β-Cyclodextrin. From the above results, it was concluded that all batches pass the evaluation tests with F4 showing the fastest wetting and Disintegration. From the data of Dissolution studies it was concluded that formulation F4 showed highest drug release in 10 minutes.

REFERENCES:

1. Thosar Milind M. Intra Oral Sprays -An Overview. Int. J. Pharm. Life Sci. 2011, 2: 1235 - 1246.
2. Ghosh Tapash K., William R. Pfister. Drug Delivery To The Oral Cavity: Molecules To Market. Boca Raton: CRC Press Taylor & Francis Group; 2005: 1 – 109.
3. Patel Priyank Et Al. Sublingual Route for The Systemic Delivery Of Ondansetron. Int. J. Drug Dev. & Res. 2011, 3: 36-44.
4. Elka Touitou, Brian W. Barry. Enhancement In Drug Delivery. Boca Raton: CRC Press Taylor & Francis Group, 2007: 173 – 214
5. Parmar VW, Thosar MM. A Comprehensive Review On: Medicated Chewing Gum"; Int. J. Res. Iny Pharm. & Biomed. Sci., **2012**, 3, 894 – 907
6. Vankani Ankit Krushnachandra, Thosar Milind M. An Overview On: Sublingual Route of Drug Delivery. Inventi Rapid: NDDS, 2014, Article ID- "Inventi: Pndds/826/13"
7. "Oral Thin Films," in Orally Disintegrating Tablet and Film Technologies, 5th ed. (Technology Catalysts International, Falls Church, VA, 2008)
8. S. S. Biradar, S. T. Bhagavati, I. J. Kuppasad. Fast Dissolving Drug Delivery Systems: A Brief Overview. The Internet Journal of Pharmacology. 2006. Volume 4 Number 2.
9. Thin Film Manufacturing Process Patent. Monosolrx.com. http://www.monosolrx.com/news_08/news_41508.html. Retrieved 2009-09-21.
10. Duchêne, D., Touchard, F., Peppas, N.A. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev. Ind. Pharm. 1988; 14: 283-318.

11. Mahrag Tur. K., Ch'ng H. S. Evaluation of possible mechanism(s) of Bioadhesion. Int. J. Pharm., 1998**,** 160, 61-74.
12. Narang N, Sharma J. Sublingual Mucosa as a Route for Systemic Drug Delivery. Int. J Pharm Sci., 2011, 3: 18 – 22.
13. Anya M. Hillery, Andrew W. Lloyd, James Swarbrick. Drug Delivery and Drug Targeting for Pharmacists and Pharmaceutical Scientists. Taylor & Francis Group, London; 2005: 168 – 187.
14. Bind A, Gnanarajan G, Kothiyal P. A Review: Sublingual Route for Systemic Drug Delivery. Int. J. Drug Res. Tech. 2013, 3: 31-36.
15. Patel NK, Pancholi SS. An Overview on: Sublingual Route for Systemic Drug Delivery. Int. J. of Res. in Pharm. & Bio. Sci. 2012, 3: 913 – 923.
16. Aghera NJ., Shah SD, Vadalia Kantilal R. Formulation and evaluation of sublingual tablets of Losartan potassium. Asian Pacific J Tropical Disease. 2012: S130-S135.
17. Raymond C Rowe, Paul J Sheskey, Marian E Quinn. Handbook of Pharmaceutical Excipients. 6th ed., London: Pharmaceutical Press and American Pharmacists Association; 2009: 210 – 214.
18. Gregorio Milani et al. Superior palatability of crushed lercanidipine compared with Amlodipine among children. Br J Clin Pharmacol. 69:2: 204 - 206.