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FORMULATE, DEVELOPMENT AND EVALUATE OF RAMIPRIL SUBLINGUAL TABLETS

VYAS ARSHAV S., PATEL KARANKUMAR M., PATEL HITESH M., SONI SARTHAK J., PATEL DHARA B.

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Corresponding Author
Mr. Arshav S. Vyas

Abstract

The objective of the current study was to develop and optimize a sublingual tablet of Ramipri which is a effective drug in the treatment of hypertension. This dosage form is associated with many advantage like quick onset of action and it by passes the liver. Especially, in case of management of Hypertensior sublingual tablets provide effective and easier way of medication. The drug and excipient compatibilit study was conducted to determine and select bland excipients for formulation. Sublingual tablets wer formulated using different diluents like mannitol DC, Lactose, Dextrose anhydrous and microcrystallin cellulose (PH 200), with different disintegrating agent's croscarmellose sodium, crospovidone (XL-10) an sodium starch glycolate. Initially the formulation was prepared by using different concentrations c croscarmellose sodium and crospovidone (XL-10) each individually, and the resulting tablet DT was foun to be high, but the expected DT was obtained when the combination of croscarmellose sodium an crospovidone were used. Similarly, the other formulation was prepared by using lower concentration c sodium starch glycolate, the DT was found to be higher, but by increasing the concentration of sodiur starch glycolate, expected DT was obtained with optimum tablet characteristic. The nine formulation were designed and evaluated for powder parameters like bulk density, Carr's index and Hausner ratic The tablets were evaluated for disintegration time, weight variation, thickness, hardness, friability an drug content. The resulting tablets were evaluated considering the disintegration time as the mai criteria. The present objective of this research has formulated a sublingual Ramipril tablet to improv bioavailability and patient compliance to therapy. Ramipril is an ACE inhibitor antihypertensive dru which inhibits the angiotensin converting enzyme and there by exerts antihypertensive activity. A direc compression technique was adapted to prepare powder blend. The formulation variables were expresse as follows; quantity of sodium starch glycolate, combination of croscarmellose sodium, crospovidone XL 10 and diluents used as mannitol (DC), lactose and dextrose anhydrous. The results obtained showed tha the mannitol (DC) and sodium starch glycolate significantly affect response variables. An optimized table formulation, containing 5.0mg of Ramipril, 30mg of MCC (PH 200) and 59mg of mannitol (DC) and 3m sodium starch glycolate, 1.8mg talc, 1mg magnesium stearate and flavor orange 0.2mg provides a shor DT of 20 sec with sufficient crushing strength and acceptable friability. The optimized formulatio compared with the conventional market formulation and showed better release compare to marke formulation.

INTRODUCTION

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. For these formulations, the small volume of saliva is usually sufficient to result in tablets disintegration in oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through sublingual blood vessels bypass the hepatic firstpass metabolic processes.[1-3]

Extremely fast tablets disintegration would be required to enhance the release of Ramipril from tablets for rapid absorption by the sublingual mucosa blood vessels. It was decided that Ramipril could be formulated into fast disintegrating tablets for sublingual administration as potential emergency treatment of hypertension.

MATERIALS AND METHODS

Materials

Ramipril, Sodium Starch Glycolate, Cross Povidone, croscarmellose sodium, Lactose, Dextrose, Mannitol, Microcrystalline Cellulose.

Methods

Direct Compression is the process by which tablets are compressed directly from mixtures of the drug and excipients without any preliminary treatment. In this process, directly compressible diluents like Lactose (anhydrous), Dextrose anhydrous, Mannitol, microcrystalline cellulose are mixed with the drug and other excipients to produce a uniform mixture and compressed into tablet. An important feature of direct compression diluent is their capacity or dilution potential. This is the amount by which they can incorporate substance, which are not directly compressible and yet produce acceptable tablets.

1. All the ingredients were weighed accurately and passed through sieve # 40.

2. Ramipril was taken and was mixed with this all ingredients in geometrical ratio in polythene bag.

3. Finally the talc was added and mixed thoroughly to get free flowing powder.

4. The blends were compressed using 6.5mm standard concave punches.

5. Following parameters were adjusted.

a) Weight : 100mg ± 10%

b) Hardness: 3 to 4 kg/cm^2

c) Disintegration time: 20-60 seconds

EVALUATION

Evaluation of Powder Blend

Angle of Repose: The angle of repose of powdered gum was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. [4]

$\theta = \tan -1 (h/r)$

Where h and r are the height and radius of the powder pile respectively

Bulk density (Do): It is the ratio of bulk volume to the total mass of the powder taken. It is measured by pouring the weighed powder into a graduated cylinder and the volume was noted.[5,6] It is given by

Do = M/Vo

Where 'M' is the mass of powder,

'Vo' is the Bulk Volume of powder; it is expressed in gm/ml.

Tapped density (Dt): It is the ratio of mass of the powder to the tapped volume of the powder. The tapped volume was measured by bulk density apparatus in which the powders were tapped for predetermined number of taps until the volume remained constant. [5,6] It is given by

Dt = M/Vt

Where 'M' is the mass of powders

'Vt' is the tapped volume of powders; it is expressed in gm/ml.

Carr's index: It indicates the ease, which a material can be introduced to flow. It is given by

C. I = (Dt-Do/Dt) x 100

Where 'Dt' is tapped density

'Do' is bulk density; it is expressed in terms of percentage.

Limit: Less than 16- Excellent flow, 16-20- Good flow, above 20-poor flow.

Hausner's ratio: This parameter was calculated by the equation[5],

H R = DT / DB

Evaluation of Tablets

Hardness: The hardness of the tablet was determined for all the formulations by using Monsanto Type hardness tester[7,9] .The hardness of all formulations was kept at 3.0 ± 1 kg/cm^2.

Friability: The friability of the tablet is not an official test but as it is required for the shipment of the product, so it was carried out by using Friabilator. The percentage friability of all the formulations was found to be not more than 0.4%which is well within the1% limit. The results of friability indicated that the tablets were mechanically stable[8,10].

Weight variation: The weight variations of the tablets were carried out by taking the Average weight of 10 tablets. The weights of the tablets were between 90.0 mg to 110.0 mg. As the weight of the tablets was 100 mg, the acceptable weight variation range is 90 mg to 110 mg (±10%). Hence all the tablet formulations were within the limits[7].

Assay: The percentage drug content of selected batch tablets was found to be between 95.11% to 96.50.0% of Ramipril, which is within the acceptable limits.

Disintegration time: Disintegration time (in seconds) for all the formulation batches was evaluated and the results are presented in table 11. Based on the study it was found that formulation B.No 4 and B. No 8 exhibited a disintegration time (in seconds) more than 100 seconds, which may be due to the presence of dextrose as diluent, though it may contain different types of disintegrating agents. If lactose is used as diluent and containing a combination of disintegrating agent such as croscarmellose sodium and crospovidone XL-10, the DT was slightly higher when compared to that of formulation B. No 5, which contained sodium starch glycolate as disintegrating agent at a concentration of 3%.The formulation B. No 3 and B. No 5 showed a low DT value among the all

formulation prepared which may be due to the presence of appropriate concentration of sodium starch glycolate as disintegrating agent. Finally it may be concluded that sodium starch glycolate at concentration of 3% with either lactose or mannitol may be considered as best diluents.

Wetting time: Similarly results to those for DT were found to be significant for wetting time. Formulation containing dextrose anhydrous as diluent and with irrespective of disintegrating agent, wetting time was found to be more than 100 seconds. Formulation B. No 5 and B. No 7 containing lactose as diluent exhibited a wetting time of 24 and 19 seconds respectively. The low wetting time of formulation B.No 7 may be due to presence of croscarmellose sodium and crospovidone XL-10 at an appropriate concentration induces capillary action there by decreases wetting time. With respect to mannitol as diluent and sodium starch glycolate as disintegrant the wetting time decreases as concentration of sodium starch glycolate increases. Formulation B. No 6, containing croscarmellose sodium and crospovidone XL-10 at a ratio of 2:2 also exhibited low wetting time values. Thus it may be concluded that formulation B. No 3.6 and 7 showed low wetting time values.

***In-vitro* release studies:** The dissolution was carried out to determine the rate of drug release at different time intervals. The sublingual tablets were subjected for dissolution study by using modified USP dissolution apparatus. The tablet was placed in the basket and the dissolution was carried out using Phosphate Buffer pH 6.8 as medium. Aliquots of 5ml were withdrawn at every 5 minutes interval and were replaced by same solution. The drug content was analyzed spectrophotometrically at 215nm against reagent blank.

Stability studies: Stability of a drug has been defined as the ability of a particular formulation, in a specific The International Conference on Harmonization (ICH) Guidelines titled 'stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the USA.

ICH specifies the length of the study and storage conditions,

Long-Term Testing: 25°C ± 2°C / 60% RH ± 5% for 12 months.

Accelerated Testing: 40°C ± C / 75% RH ± 5% for 6 months. Stability studies were carried out at 25°C/ 60% RH and 40°C/ 75% RH for the selected formulations for six months.

Procedure

The selected formulations were packed in the strip packaging, which were packed in the card board box and labeled. They were then stored at 45°C, 37°C, 40°C/ 75% RH and Room Temp. Kept for three months and evaluated for their physical appearance, drug content and drug release at specific intervals of time per ICH Guide lines. The present study was aimed at the formulation of Ramipril sublingual tablet. The key advantage of this drug is its specificity of action, high safety and excellent efficacy.

RESULTS AND DISCUSSION

Drug release profile

The dissolution study was carried out using 100ml of pH 6.8 phosphate buffer dissolution medium at 50rpm at 37°C ± 0.5 °C. Formulations Batch no 03 and 05, showed rapid dissolution rate, the percentage cumulative drug release (%CDR) after 5 minutes found to be more than 80% and complete dissolution was achieved within 15minutes. Thus it may be concluded that formulation B. no 3 and 5 may be considered as best formulation with respect to in vitro drug release profile.

Optimized formula

Based on pre-compression parameters formulation B. No 3 and 6 was considered as best formulations. With respect to post-compression parameters like disintegration time, wetting time and dissolution study (in vitro) formulation B.No 3, 5, 6 and 7 was considered as best formulation. From the above discussion one can infer that formulation B. No 3 and 6 can be considered as best formulations as sublingual tablet containing Ramipril as the model drug. As such formulation B.No 6 contains mannitol as a diluent and a combination of disintegrants (such as croscarmellose sodium and crospovidone XL-10) may not be cost effective thus, formulation B. No 3 containing a single disintegrating agent along with mannitol DC as diluent may be considered as best formulation among the all nine batches.

Hence formulation B.No 3 and 6 were subjected to further stability studies.

Stability study

In present study short term physical stability and drug content and dissolution profile were carried out of formulation batch no 03, and 06.

(a) Physical stability

There was no significant difference in the colour and visual appearance in all the tablets of different batches in one month stability studies.

(b) Disintegration

There was no significant difference in the disintegration time in all the batches of tablets.

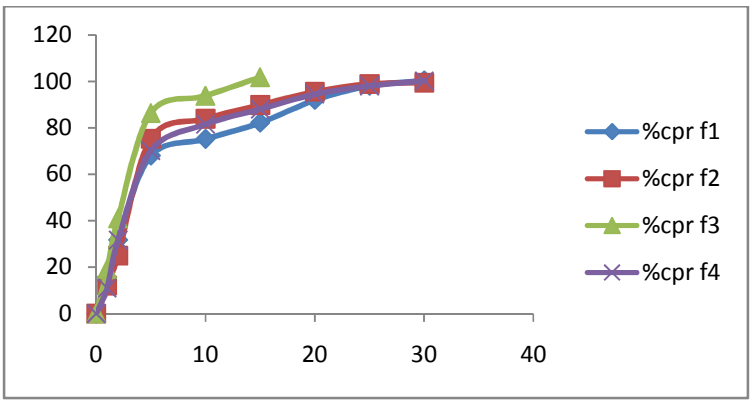
(c) Drug content

The results of drug content in all the formulations inferred no significant deviation from the initial values this indicates the stability of drug in all the batches of tablets.

(d) Dissolution profiles

Dissolution profiles were carried out for the batch no 03, and 06 at the intervals of one months. There was no significant variation in the dissolution profiles with respect to the above two batches of the tablets.

In-Vitro drug release profile Time Vs % of Cumulative drug release Batch: F1-F4



In-Vitro drug release profile Time Vs % of Cumulative drug release Batch: F5-F9

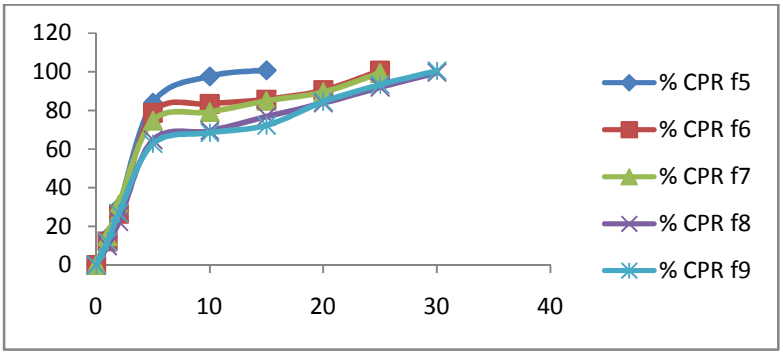


Table 1: Formulations of Sublingual Tablets of Ramipril

Formulation Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ramipril	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
MCC	30	30	30	30	30	30	30	30	30
Lactose	-	-	-	-	59	-	58	-	-
Mannitol	61	60	59	-	-	58	-	-	-
Dextrose Anhydrous	-	-	-	59	-	-	-	58	61
SSG	1	2	3	3	3	-	-	-	-
CPV	-	-	-	-	-	2	2	2	1
CSS	-	-	-	-	-	2	2	2	1
Talc	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Mg. Stearate	1	1	1	1	1	1	1	1	1
Flavour	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
TOTAL(mg)	100	100	100	100	100	100	100	100	100

Table 2: Physical properties of Powder Blend for ramipril tablets

Batch No.	Angle of Repose(θ)	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Compressibility Index (%)	Hausner Ratio
F1	18.99	0.515	0.585	13.59	1.135
F2	17.99	0.51	0.595	16.66	1.16
F3	16.49	0.515	0.585	13.59	1.13
F4	15.60	0.52	0.595	14.42	1.14
F5	35.7	0.505	0.605	19.80	1.198
F6	17.6	0.505	0.595	17.82	1.18
F7	29.2	0.525	0.592	12.76	1.127
F8	19.7	0.515	0.605	17.47	1.17
F9	18.2	0.532	0.605	13.72	1.14

Table 3: Disintegration time of optimized batch No. 03 and 06 after stability study

TIME IN DAYS	RT 37ºC	
BATCH NO.	03	06
0	20	39
30	21	37
60	-	-

Table 4: % Drug Content of optimized batch No. 03 after stability study

TIME IN DAYS	RT 37ºC	
BATCH NO.	03	06
0	97.81	96.21
30	98.01	96.52
60	-	-

Table 5: Dissolution Profile of optimized batch No. 03 after stability study

TIME(MIN)	% CUMULATIVE DRUG RELEASE		
	Initial	**30 Days**	**60 Days**
1	19.1	18.46	Awaiting
2	41.03	39.92	-
5	86.38	83.91	-
10	93.74	96.56	-
15	101.8	100.7	-

Table 6: Dissolution Profile of optimized batch No. 06 after stability study

TIME(MIN)	% CUMULATIVE DRUG RELEASE		
	Initial	30 Days	60 Days
1	12.29	14.9	Awaiting
2	26.4	31.26	-
5	78.79	74.71	-
10	83.36	79.09	-
15	85.65	84.89	-
20	90.43	89.43	-
25	100.6	99.39	-

Conclusion:

The concept of sublingual tablets containing Ramipril offers a suitable and practical approach in serving the desired objective of management of The excipients used in the formulation were inexpensive and are easily available. Most of the excipients used in formulation are water-soluble and hence have a better patient acceptability.

The present work of formulating a sublingual tablet containing Ramipril was successful in terms of reducing manufacturing difficulties, cost and providing a better patient compliance with effective medication and overcoming disadvantages of aerosols and oral dosage form.

It has been observed from the above study that excipients like mannitol, microcrystalline cellulose, sodium starch glycolate and flavor orange were found to be ideal excipients and effective for formulating sublingual tablets.

Sublingual tablets provide several advantages especially when administered to children and elderly patients. Rapid absorption into the systemic circulation within short period time may be achieved.

The sublingual tablets of B. No 03 was contain 5mg of Ramipril 30mg of MCC PH

200 and 59mg of mannitol (DC) and sodium starch glycolate 3mg, talc 0.2mg and flavor orange 0.2mg considered to be the best among all other nine batches of tablets since it exhibited a good dissolution profile, disintegration time, appearance, uniformity of drug content, taste and further good stability and In vivo absorption profile.

REFERENCES

1. Mutasem M, Rawas-Qalaji F, Estelle R, Simons and Keith J. Fast-disintegrating Sublingual Tablets: Effect of Epinephrine Loadon Tablet Characteristics. AAPS. 2006;7(2):E1-E7.

2. Birudaraj R, Berner B, Sen S. Buccal permeation of buspirone: mechanistic studies on transport pathways. J Pharm Sci. 2005; 94: 70-78.

3. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R and Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 bete-estradiol. Obst Gyn.1997; 89: 340-345.

4. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors; 1986; 211-233.

5. Alfred Martine, physical Pharmacy, 4th edition, BI Waverly pvt Ltd, New Delhi, 1996, 423-431.

6. Jain, S.K., Awasthi, A.M., Jain, N.K., Agrawal, G.P., and Calcium silicate based microspheres of DCPT155 for gastro retentive floating drug delivery: Preparation and in vitro characterization. J. Control. Rel.2005, 107, 300– 309.

7. Pharmacopoeia of India. New Delhi: Ministry of Health and Family Welfare, Government of India, Controller of Publications; 2007.

8. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy; Philadelphia, PA: Lea and Febiger; 1987; 317- 318.

9. The United State of Pharmacopoeia 24/ Nf19 Asian Edition, The official compendia of standard United States pharmacopoeial convection Inc. Rockville. 1995; 1015, 1016, 1791.

10. Chaudhari PD. Formulation and Evaluation of fast dissolving tablet of famotidine Indian Drug. 2005; 42(10): 641-649.