International Journal of Current Trends in Pharmaceutical Research

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Formulation and *In-vitro* Evaluation of Ergotamine Tablets for Buccoadhesive Drug Delivery System

Gampa Vijaya Kumar[1], Dr. G.S. Valluri[2], Thota Karunakar[3]

[1]*Professor and Head, Department of Pharmacy, KGR Institute of Technology and Management, Rampally, Kesara, Rangareddy, Telangana, India.*
[2]*Professor, KGR Institute of Technology and Management, Rampally, Kesara, Rangareddy, Telangana, India.*
[3]*KGR Institute of Technology and Management, Rampally, Kesara, Rangareddy, Telangana, India*.

A B S T R A C T

Ergotamine was formulated as buccal tablets to improve its bioavailability by avoiding first pass metabolism.HPMC K4M, HPMC K15M, HPMC K100M were selected as polymers various formulations were prepared by using these polymers.The precompression blend of Ergotamine Buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio and all the results indicated that the blend was having good flow nature and better compression properties. The in-vitro drug release studies were performed for the formulations which were shown desired drug release.The formulations prepared with HPMC K100M in the concentration of 8mg (F8) was showing 92.06% drug release. The swelling studies were performed for the formulations which were shown desired swelling and the value was found to be 68.5 % in 8 hours. The selected formulations F8 formulation was showing maximum flux value and permeability coefficient value i.e.,389.42 (µg.hrs-1cm-2) and 0.111 (cm/h) respectively.

Keywords: Ergotamine, Buccal tablets, HPMC K4M

A R T I C L E I N F O

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Article History: Received 18 April 2017, **Accepted** 21 May 2017, **Available Online** 15 July 2017

***Corresponding Author**
Dr. Gampa Vijaya Kumar
Professor and Head, Dept. of Pharmacy, KGR Institute of Technology and Management, Rampally, Kesara, Rangareddy, Telangana, India
Manuscript ID: IJCTPR3473

PAPER-QR CODE

Citation: Gampa Vijaya Kumar, *et al.* Formulation and *In-vitro* Evaluation of Ergotamine Tablets for Buccoadhesive Drug Delivery System. *Int. J. Curnt. Tren. Pharm, Res.*, 2017, 5(4): 149-154.

1. Introduction

Buccoadhesive Drug Delivery

The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption. Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect). Ergotamine tartrate is a Ergot alkaloid. It is an antimigraine and sympatholytic drug which is commonly used to treat migraine. Its dose is not more than 8mg in a day. It metabolises in liver by largely undefined pathways and 90% of the metabolites are excreted in the bile with the half life of about 4hrs. The concept of formulating fast dissolving tablet of Ergotamine tartrate offers a suitable and practical approach in desired objective of fast disintegrating & dissolution characteristics with increased bioavailability.

2. Materials and Methods

Ergotamine, HPMC GRADES**,** Magnesium stearate, Talc, Microscrystalline cellulose all the chemicals used were lab grade

Formulation and preparation of tablets

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. HPMCK4M, HPMCK15M, HPMCK100M are the mucoadhesive and biodegradable polymers used in this preparation of buccal mucoadhesive drug delivery systems.

Ergotamine was mixed manually with different ratios of HPMCK4M,HPMCK15M,HPMCK100M, Microcrystalline Cellulose as diluent for 10 min. In every formulation constant amount of PVPK30 was added as binding agent. The blend was mixed with talc and magnesium stearate for 3-5 min. Then the powder blend was compressed into tablets by the direct compression method using 8 mm flat faced punches. The tablets were compressed using 8 station Cemach rotary tablet-punching machine. The weight of the tablets was determined using a digital balance and thickness with digital screw gauge. Composition of the prepared bioadhesivebuccal tablet formulations of Ergotamine were given in Table 1.

Evaluation of post compression parameters for prepared Tablets:

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

3. Results and Discussions

Standard Graph of Ergotamine at λ_{max} 272nm:

Standard stock solution of pure drug containing 100 mg of Ergotamine 100mL was prepared using buffer 6.8 pH phosphate buffer solution. The working standards were obtained by dilution of the stock solution in 6.8 pH phosphate buffer. The standard curve for Ergotamine was prepared in concentration range 10-50 µg/mL at the selected wavelength 272nm. Their absorptivity values were used to determine the linearity. Solutions were scanned and beer lamberts law limit was obeyed in concentration range of 10, 20, 30, 40, 50µg/mL. The same procedure is repeated by using pH 7.4 phosphate buffer.

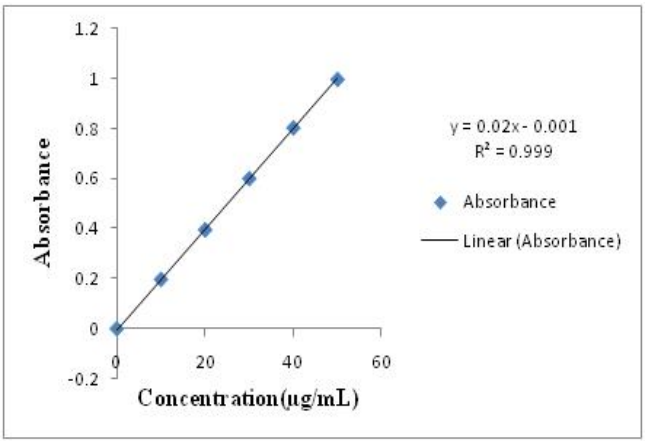

Figure 1: Standard graph of Ergotamine in 6.8 pH phosphate buffer

Evaluation:

Characterization of Precompression Blend:

The precompression blend of Ergotamine Buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Evaluation of Buccal Tablets:

Physical Evaluation of Ergotamine Buccal tablets:

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 4.4. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.6 to 5 kg/cm2 and the friability values were less than 0.561% indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 3.71-3.91cm. All the formulations satisfied the content of the drug as they contained 98-100% of Ergotamine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

In-vitro release studies:

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm

glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 272nm.

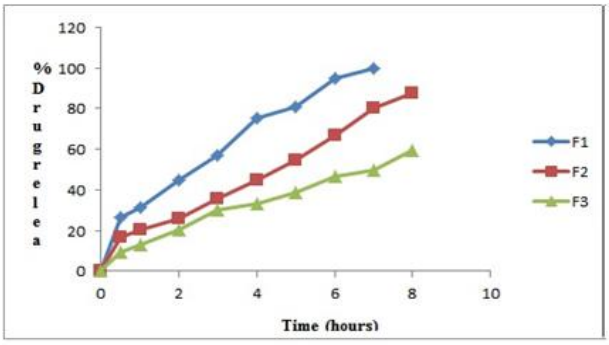

Figure 2: In-vitro dissolution data for formulations F1 - F3 by using HPMC K4M Polymer

From the above graphs it was evident that HPMC K 4M in the concentration of 8 mg (F2), is showing better result 87.7% drug release when compared with other two ratios.

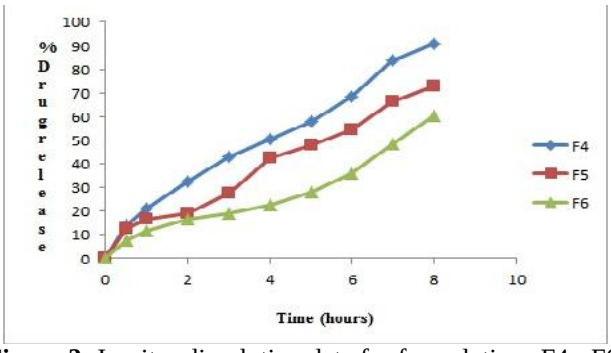

Figure 3: In-vitro dissolution data for formulations F4 - F6 by using HPMC K15 M Polymer

From the above graphs it was evident that HPMC K 15 M in the concentration of 4 mg (F4), is showing better result 90.90% drug release when compared with other two ratios. As the concentration of polymer increases the retarding of drug release also increased. Hence they were not considered.

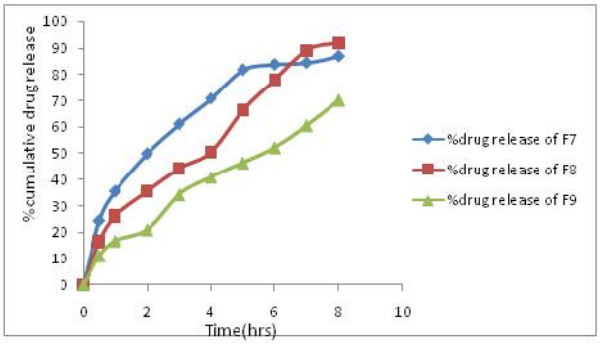

Figure 4: In-vitro dissolution data for formulations F7 – F9 by using HPMC K100M Polymer

From the above graphs it was evident that HPMCK100M in the concentration of 8mg (F8), is showing better result 92.06% drug release when compared with other two concentrations.

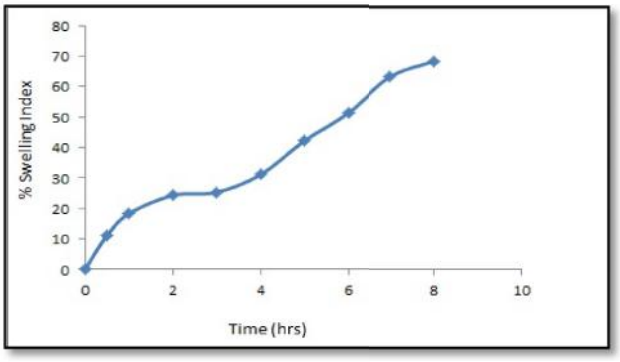

Figure 5: Graph Showing Swelling Index Values

The swelling studies were performed for the optimized formulation which was shown desired drug release. Swelling behavior of a buccal system was essential for uniform and prolonged release of drug and proper bioadhesion. The formulation containing HPMCK100M was shown good swelling index.

Release kinetics: Data of invitro release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Ergotamine release from buccal tablets. The data was fitted into various kinetic models such as zero,first order kinetics, Higuchi and Karsmeyer Peppas mechanisms and the results were shown in below table. From the above release kinetics data it was evident that the formulation was following zero order kinetics with regression value of 0.978 and it is following non fickian diffusion mechanism.

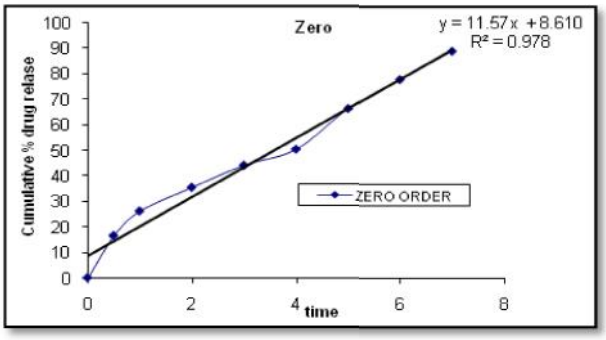

Figure 6: Zero order kinetics

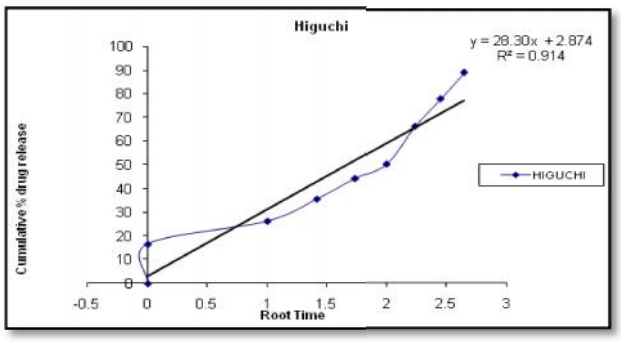

Figure 7: Higuchi plot

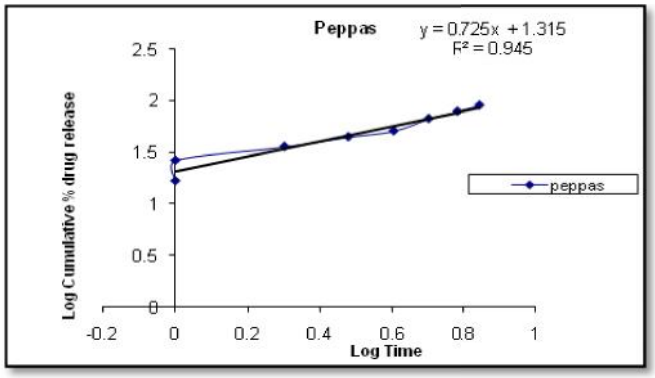

Figure 8: Peppas plot

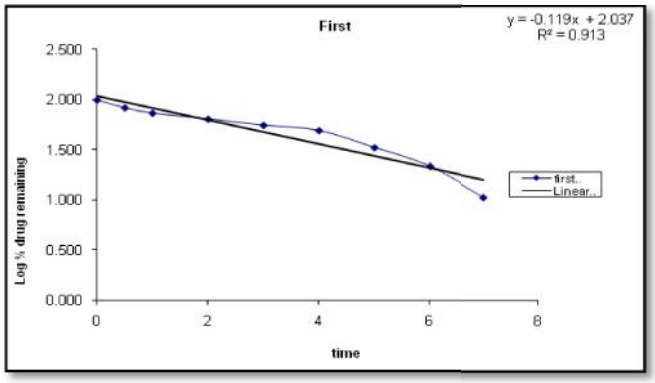

Figure 9: First order release kinetics

Figure 10: FTIR spectrum of pure drug

Discussion: The above figure is the FT-IR spectrum of the pure drug by which the compatibility of drug to all other excipients can be known by the wave numbers which are present.

Figure 11: FTIR spectrum of optimized formulation

Discussion:
The above figure is the FT-IR spectrum of the optimized formula by which the compatability of drug to all other excipients can be known by the wave numbers which are present.

5. Conclusion

Ergotamine was formulated as buccal tablets to improve its bioavailability by avoiding first pass metabolism.HPMC K4M, HPMC K15M, HPMC K100M were selected as polymers various formulations were prepared by using these polymers. The precompression blend of Ergotamine Buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio and all the results indicated that the blend was having good flow nature and better compression properties. The swelling studies were performed for the formulations which were shown desired drug release. The formulations prepared with HPMC K100M in the concentration of 8mg (F8) was showing better result 92.06% drug release.The swelling studies were performed for the formulations which were shown desired drug release and the value was found to be 68.5 % in 8 hours. The selected formulations F8 formulation was showing maximum flux value and permeability coefficient value i.e.,389.42 (µg.hrs-1cm-2) and 0.111 (cm/h).

Table 1: Composition of buccal tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	2	2	2	2	2	2	2	2	2
HPMCK4M	4	8	12	-	-	-	-	-	-
HPMCK15M	-	-	-	4	8	12	-	-	-
HPMC K 100M	-	-	-	-	-	-	4	8	12
MCC pH 102	70	66	62	70	66	62	70	66	62
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight (mg)	80	80	80	80	80	80	80	80	80

Table 2: Standard graph values of values of Ergotamine in 6.8 pH phosphate buffer

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.198
3	20	0.396
4	30	0.601
5	40	0.804
6	50	0.998

Table 3: Physical properties of precompression blend

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25.10°	0.53±0.01	0.59±0.01	9.43±0.12	1.09±0.02
F2	25.43°	0.54±0.03	0.60±0.02	9.40±0.13	1.10±0.01
F3	25.41°	0.54±0.02	0.58±0.03	10.01±0.19	1.13±0.06
F4	26.40°	0.51±0.01	0.61±0.06	10.11±0.02	1.16±0.01
F5	27.12°	0.58±0.03	0.63±0.03	10.34±0.13	1.17±0.03
F6	25.31°	0.59±0.03	0.64±0.04	10.12±0.34	1.11±0.06
F7	26.11°	0.56±0.01	0.63±0.01	9.93±0.11	1.13±0.03
F8	26.15°	0.53±0.03	0.58±0.03	10.13±0.02	1.12±0.01
F9	25.43°	0.54±0.03	0.60±0.02	9.40±0.13	1.10±0.01

All the values represent mean ± Standard deviation (SD), n=3

Table 4: Physical Evaluation of Ergotamine Buccal tablets

Formulation code	Weight variation (mg)	Thickness (cm)	Diameter	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	83.20	3.76±0.01	8.12±0.01	4.5±0.7	0.420	99±0.12
F2	84.30	3.74±0.04	8.14±0.02	4.2±0.5	0.341	99±0.3
F3	81.10	3.71±0.01	8.01±0.01	3.6±0.6	0.363	100±0.1
F4	84.20	3.80±0.06	8.03±0.03	4.8±0.5	0.561	100±0.3
F5	85.22	3.81±0.04	8.04±0.04	3.8±0.4	0.482	99±0.6
F6	84.12	3.74±0.05	8.09±0.05	4.4±0.6	0.513	99±0.4
F7	79.33	3.76±0.03	8.11±0.03	5 ± 0.1	0.412	98±0.9
F8	80.22	3.71±0.04	8.09±0.06	4.6±0.2	0.432	99±0.1
F9	80.10	3.73±0.03	8.03±0.02	4.0±0.3	0.512	100±0.1

Table 5: In-vitro dissolution data for formulations F1 – F9

Time(hrs)	% Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	26.73	16.73	9.4	14.23	12.56	7.73	24.4	16.56	11.06
1	31.06	20.4	13.23	20.9	16.57	11.56	35.56	26.23	16.73
2	44.9	25.9	20.4	32.73	18.9	16.56	49.9	35.56	21.06
3	57.06	35.56	29.9	42.9	27.73	18.9	61.06	44.23	34.4
4	75.56	44.9	33.23	50.4	42.4	22.73	70.73	50.56	41.06
5	81.06	54.4	38.73	57.73	47.9	28.23	81.73	66.56	46.56
6	94.9	66.56	46.56	68.56	54.4	36.06	83.73	78.23	52.4
7	99.56	79.9	49.9	83.73	66.56	48.4	84.4	89.4	60.73
8	-	87.73	59.56	90.9	72.73	60.4	86.85	92.06	70.4

Table 6: Swelling index of optimized formulation (F8)

Time (hrs)	Swelling Index (%)
	F8
0	0
0.5	11.1
1	18.3
2	24.3
3	25.3
4	31.11
5	42.2
6	51.3
7	63.4
8	68.5

Each value represents the mean ± SD (n=3)

Table 7: Release kinetics

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
16.56	0.5	0.000	1.219	0.000	1.921
26.23	1	1.000	1.419	0.000	1.868
35.56	2	1.414	1.551	0.301	1.809
44.23	3	1.732	1.646	0.477	1.746
50.56	4	2.000	1.704	0.602	1.694
66.56	5	2.236	1.823	0.699	1.524
78.23	6	2.449	1.893	0.778	1.338
89.4	7	2.646	1.951	0.845	1.025
92.06	8	2.828	1.964	0.903	0.900

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