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FORMULATION DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE BUCCAL DELIVERY OF TERBUTALINE SULFATE

Tirumala Devi Kolli[1]*, Anand Vardhan Dommeti[2], Prasada Rao Manchineni[3]

[1]Professor, Department of Pharmaceutics, MAM College of Pharmacy, Kesanupalli, Narasaraopet, Palnadu, Andhra Pradesh, India-522601.

[2]Student, Department of Pharmaceutics, MAM College of Pharmacy, Kesanupalli, Narasaraopet, Palnadu, Andhra Pradesh, India-522601.

[3]Professor & Principal, Department of Pharmaceutics, MAM College of Pharmacy, Kesanupalli, Narasaraopet, Palnadu, Andhra Pradesh, India-522601.

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***Corresponding Author**
Tirumala Devi Kolli

Professor, Department of Pharmaceutics, MAM College of Pharmacy, Kesanupalli, Narasaraopet, Palnadu, Andhra Pradesh, India-522601.

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ABSTRACT

Buccal tablets of terbutaline sulphate were developed using bioadhesive polymers along with other excipients to produce modern formulations. In this study, the effects of bioadhesive polymers such as HPMC K4M, HPMC K15M, HPMC K100M were evaluated. The tablets were prepared by direct compression and characterized for thickness, hardness, weight variation, friability, drug content, in-vitro drug release. In-vitro drug release studies were conducted using 900 ml of Phosphate buffer at 50 rpm in a USP type II dissolution apparatus for 12 hours. The results indicated that drug release increased with higher concentrations of cellulose derivatives (HPMCK100M), while it decreased with increasing amounts of MCC. Various kinetic models were applied to analyze the release kinetics of the dosage form. Overall, the physical properties of the formulated buccal tablets were within acceptable limits. Whereas from the dissolution studies it was evident that the formulation (F7) showed better and desired drug release pattern i.e., 98.76 % in 12 hours. It followed zero order release kinetics mechanism.

KEYWORDS: Controlled Release, Buccal delivery, Terbutaline sulfate, swelling index, Bioadhesive polymers.

INTRODUCTION

Bioadhesion is defined as the phenomenon in which natural or synthetic polymers adhere to a biological substrate, primarily through interfacial interactions such as electrostatic attraction. This property enables polymers to remain bound to biological surfaces for prolonged periods, making them valuable in drug delivery applications.

Among the various drug delivery routes, the oral route remains the most preferred by both patients and healthcare professionals due to its convenience and non-invasive nature. However, oral administration has significant limitations, including first-pass hepatic metabolism, poor solubility, and enzymatic degradation in the gastrointestinal (GI) tract. These challenges make it unsuitable for certain classes of drugs, especially proteins and peptides. To overcome these drawbacks, alternative transmucosal routes have been explored.

Transmucosal drug delivery systems—utilizing nasal, rectal, oral, vaginal, and ocular mucosa—offer several advantages over conventional oral administration. These include bypassing first-pass metabolism, avoiding presystemic elimination in the GI tract, and providing rapid onset of action. While the nasal route has been investigated extensively, concerns such as mucosal irritation, ciliary dysfunction, and potential irreversible damage limit its long-term applicability.

In contrast, the oral cavity provides an attractive and commercially established site for transmucosal drug delivery. Drugs such as nitroglycerin (sublingual tablets for angina) and fentanyl (transmucosal buccal formulations, e.g., Actiq®, Abbott Laboratories, USA) have demonstrated clinical success. Patients also report high satisfaction with oral transmucosal delivery due to ease of use and faster therapeutic effects.

The oral mucosa is well-suited for local as well as systemic therapy. It possesses high vascularization, permeability, and a rich aqueous environment that facilitates drug absorption. Additionally, it has a short healing time (approximately one week after injury), enhancing its suitability as a drug delivery site. Local therapies include treatments for conditions such as gingivitis, oral candidiasis, xerostomia, oral lesions, and dental caries, whereas systemic

delivery through the buccal route has been employed in the management of angina and asthma.

The buccal mucosa, in particular, provides unique advantages for drug delivery. It enables the administration of proteins and peptides that would otherwise be degraded in the acidic environment of the stomach or undergo extensive first-pass hepatic metabolism. Its favorable characteristics—such as high vascular supply, flexibility in dose removal, rapid epithelial turnover, and improved patient compliance—make the buccal route a promising alternative to conventional drug administration pathways.

MATERIAL AND METHODS

"Terbutaline sulphate collected by Themes Laboratories PVT LTD, Mumbai (India), as a free gift study and purchased from CDH dealers, the polymers (HPMC K100 M, Ethyl cellulose, Carpool 934-P and Na-CMC) and excipients (magnesium stearate and lactose monohydrate) All other reagents and excipients were of pharmaceutical grade". Methods: "Preparation of buccal tablets of terbutaline sulphate" Buccal tablets Specific amounts of polymers or excipients like medications were formulated, First, so all polymers are weighed correctly but tinctured though as well as their composition or intensity, and then lactose mixture was applied to both the "mixture and triturate for 2 minutes. Lactose is often used as bulkning agent. Magnesium separate as a lubricant was applied to the mixture following thorough grinding", but instead triturated afterwards. Dry granulation technique besides tablet preparation had been accompanied, in which the mixture has been condensed compacted rotary loading frame with such a continual force applied as well as the same climate has been maintained for certain formulations. "Total weight of per tablet was 60 mg including drug.

Pre-formulation study

Bulk density

The mass--volume ratio of an untapped powder sample is known as bulk density. In g/ml, the bulk density is expressed. Both the powder particle density and the powder particle arrangement affect the bulk density. The bulk density affects how the sample is prepared and stored. Below is the mathematical representation.

Bulk density = weight of the drug /bulk volume

Tapped density

When bulk powder is tapped for density, it is mechanically tapped in a graduated cylinder

until a volume difference is noticed. Here, the tapped density is computed by dividing the mass by the powder's ultimate volume.

Tapped density = weight of the granules/ tapped volume

Angle of repose

It provides a sense of how easily granules or bulk solids can flow. The flowability of powders can be attributed to various factors, including the surface area, shape, and size of the particles. The powder's flowability varies with the environment and is easily adjustable. The following formula was used to get the angle of repose.

$$\theta = \tan^{-1} h/r$$

Where,

θ = angle of repose

h = height of the formed cone

r = radius of the circular base on the formed cone.

Carr's index

It is among the most crucial parameters for describing the granule's nature.

Carr's index (%) = (tapped density – bulk density / tapped density) x 100

Hausner's ratio

Determining the granule flow behavior in the presence of various polymer compositions is a crucial characteristic. This can be determined by the following formula:

Hausner's ratio = tapped density / bulk density

Good flow is indicated by values less than 1.25, and poor flow is indicated by values more than 1.25.

Post-compression study of formulated tablets

Weight variation test

Twenty tablets were picked randomly from each formulation and weighed separately using a digital balance (Shimadzu AUY 220, Uni Bloc, Germany). Mean values were calculated together with average weights. Approximately 5% deviation is the maximum allowed by the Indian Pharmacopeia (IP).

Tablet thickness test

Using Vernier callipers, the thickness of 20 randomly chosen tablets from each formulation is measured in order to assess the consistency and physical dimensions of the tablet.

Hardness test

The hardness of the tablets was measured using a Monsanto hardness tester. One of the key elements that plays a big part in transportation is hardness. Using a Pfizer hardness tester, the ten tablets hardness was determined. It is stated as kg/cm^2.

Formulation composition for tablets

Formulation No.	Terbutaline Sulfate (Mg)	HPMC K4M (Mg)	HPMC K15 (Mg)	HPMC K100M (Mg)	Mg. Stearate (Mg)	Talc (Mg)	MCC (Mg)
F1	8.5	20	15	10	2.5	2.5	1.5
F2	8.5	10	20	15	2.5	2.5	1.5
F3	8.5	15	20	10	2.5	2.5	1.5
F4	8.5	10	15	20	2.5	2.5	1.5
F5	8.5	15	10	20	2.5	2.5	1.5
F6	8.5	20	10	15	2.5	2.5	1.5
F7	8.5	12	18	15	2.5	2.5	1.5
F8	8.5	18	12	15	2.5	2.5	1.5
F9	8.5	15	18	12	2.5	2.5	1.5

RESULTS AND DISCUSSION

Pre-compression characterization: The tapped density, bulk density, Hausner's ratio, Carr's index and angle of repose is the pre-compression characterization of buccal tablet. Angle of repose (θ): "The fractional force in the powder can be measured by the angle of repose. Angle of repose was obtained by fixed funnel method.

Angle of repose can be calculated by using following formula":

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

Where: θ= Angle of repose

h = Height of heap in cm

r = Radius of heap in cm

Bulk density: Weighed accurately 10 gm of powder and transferred into 100 ml measuring cylinder. Carefully record the level of unsettled volume of powder. Calculate bulk density in gm/ml.

Tapped density: Weighed accurately 10 gm of powder and transferred into 100 ml graduated cylinder. After that 100 tapped to the cylinder was applied and then volume of powder was measured carefully.

Carr's index: The Carr / compressibility index is the test to evaluate the propensity to compress the powders.

"Hausner's ratio:" It is associated with the flow capacity of powder or granular material. Hausner's Ratio = Tapped Density / Bulk Density

Pre-formulation parameters of powder blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	23.03	0.54	0.54	15.12	1.09
F2	25.11	0.53	0.55	16.77	0.99
F3	22.36	0.51	0.51	17.93	1.05
F4	23.42	0.52	0.54	15.72	1.11
F5	24.79	0.54	0.56	15.26	1.12
F6	22.11	0.55	0.57	16.44	1.08
F7	23.02	0.52	0.55	17.61	1.05
F8	24.73	0.52	0.52	16.34	1.01
F9	22.45	0.51	0.51	17.12	1.03

Post Compression Parameters

Thickness: That diameter or diameter of both the tablets of any and all formulations with vernier caliper is established.

Tablet weight variation: Each single tablet in such a batch is within reasonable parameters of standard weight or weight variations. Weight regulation is dependent upon a 20 tablet study. Twenty tablets with matrix was picked randomly and weighted correctly but use an electronic balance. Those outcomes of 20 determinations were presented as average value.

Hardness: Tablet hardness has been evaluated with a toughness test device (Monsanto Type). For dimensional characteristics a tablet hardness of about 4-6 kg / cm2 is deemed sufficient.

Friability: That tablets' friability has been assessed using a roche friabilator. Tablets with a known weight (W0) or a sample of 10 tablets have been subtracted for a fixed time in either a drum (100 revolutions) but also weighed again (W). Percentage friability has been calculated from weight loss. This same weight loss should not be greater unlike 1 % w/w.

% Friability = (W0 −W)/W0 ×100

Drug content: 10 tablets Weighed but dried, powder equal to 10 mg the drug being extracted and dissolved in phosphate buffer, creating 10 ml of distilled water of amount. After which a solution of 10 ppm became formulated and absorption spectrum determined at 280.40 nm by using UV spectrophotometer.

In-vitro bioadhesion study: There in laboratory that equipment used during bioadhesion research was assembled. A intensity of both the tablet's mucoadhesion were calculated.

Table: Post compression parameters.

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	61	4.5	0.52	1.8	98.52
F2	60	4.3	0.54	1.9	99.63
F3	59	4.4	0.53	1.8	97.14
F4	61	4.5	0.55	1.8	98.02
F5	62	4.4	0.56	1.8	98.11
F6	61	4.3	0.55	1.8	98.63
F7	63	4.6	0.54	1.8	98.14
F8	57	4.5	0.56	1.8	99.53
F9	59	4.4	0.55	1.7	97.15

In-vitro drug release characteristics: Utilising USP type II dissolution apparatus outfitted to paddles at 37oC ±0,5oC with the a rpm of 50, this same drug release from both the buccal tablets has been assessed. That research was conducted then using dissolution medium of 900 ml with Phosphate buffer. Analysis of the breakdown took place in triplicate, this same sink circumstances for all of the other preparations are maintained. During daily intervals, a 5 ml sample aliquot was collected, screened then spectro-photo metrically checked 280.40 nm. Drug release kinetics: That data collected were incorporated into a) Zero order kinetics; b) First order kinetics; c) Higuchi's square root system or d) Korsemeyer and peppas design for evaluate each function of both the medication release rate kinetics for the dosage size. Statistical analysis will be carried out on information gathered from of the treatment duration (student’s t-test) And

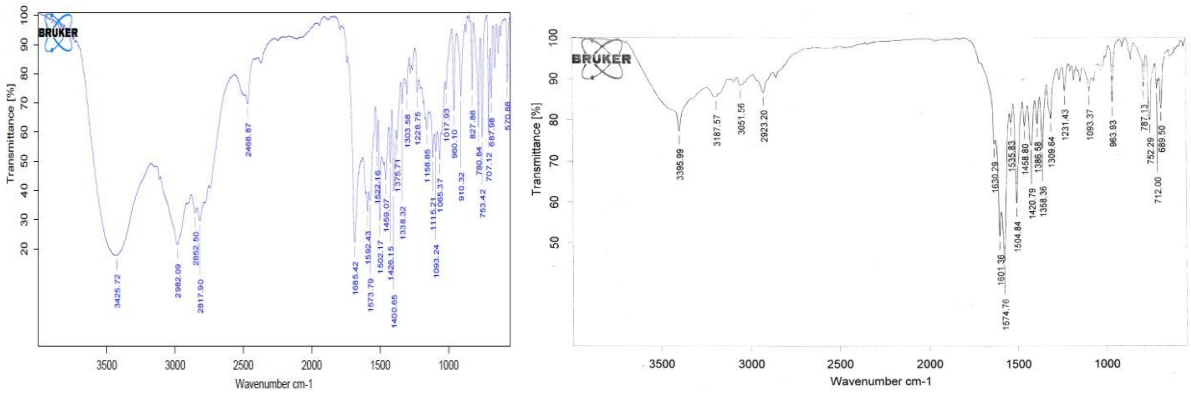

Table 8.4: Dissolution Data of Terbutaline sulfate Tablets Prepared With HPMC K4M (F1-F3) & HPMCK15M (F4-F6) In Different Concentrations.

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	6.03	8.85	8.14	7.16	7.13	8.12
1	13.54	14.53	13.52	13.54	12.10	15.35
2	19.82	23.42	19.92	19.90	17.86	21.37
3	24.93	28.92	26.75	25.12	25.10	26.15
4	32.52	39.13	39.76	31.36	34.48	31.58
5	41.67	45.96	45.21	39.98	41.24	39.94
6	49.34	53.91	54.32	47.93	49.91	47.12
7	58.86	60.43	63.14	52.16	57.13	56.87
8	63.74	69.12	71.52	60.92	65.21	63.92
9	70.92	78.32	77.13	68.34	71.10	74.14
10	78.07	82.16	82.16	74.19	79.93	79.81
11	84.43	87.12	86.52	81.86	84.21	85.13
12	89.12	92.57	93.21	87.13	90.32	92.12

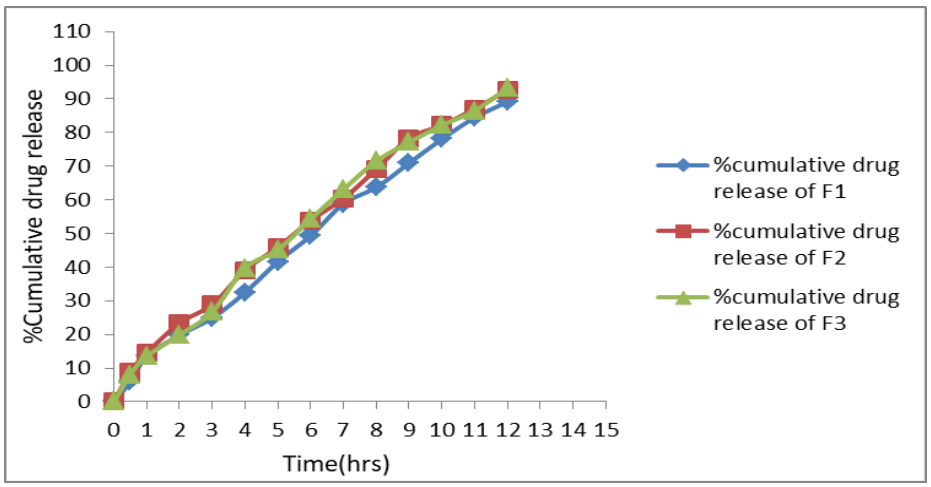

Fig. 8.4: Dissolution profile of Terbutaline sulfate (F1, F2, F3 formulations).

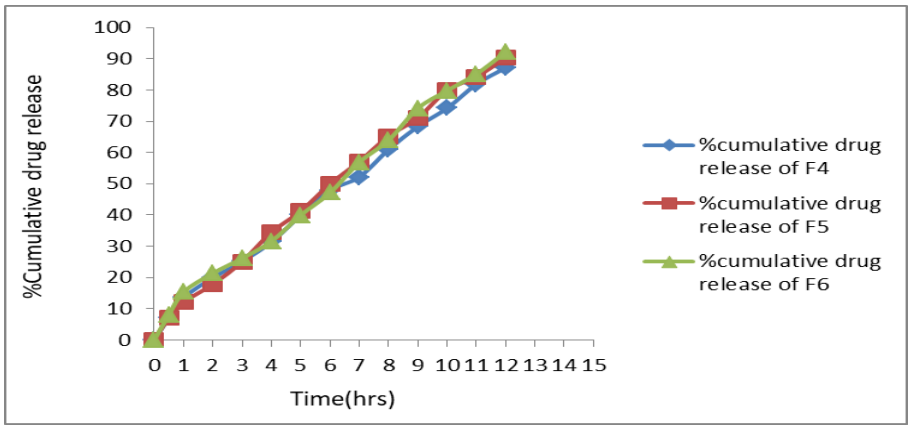

Fig: Dissolution profile of Terbutaline sulfate (F4, F5, F6 formulations).

Table: Dissolution Data of Terbutaline sulfate Tablets Prepared With HPMCK100M In Different Concentrations.

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	F8	F9
0	0	0	0
0.5	7.16	7.14	8.20
1	12.14	12.03	13.81
2	19.25	16.34	17.34
3	27.24	22.16	22.23
4	38.92	29.24	27.18
5	47.24	37.91	38.14
6	55.83	48.23	46.92
7	62.27	55.20	52.12
8	69.15	62.14	59.91
9	78.71	70.91	64.06
10	84.13	78.35	72.87
11	92.95	82.34	79.13
12	98.76	89.23	85.92

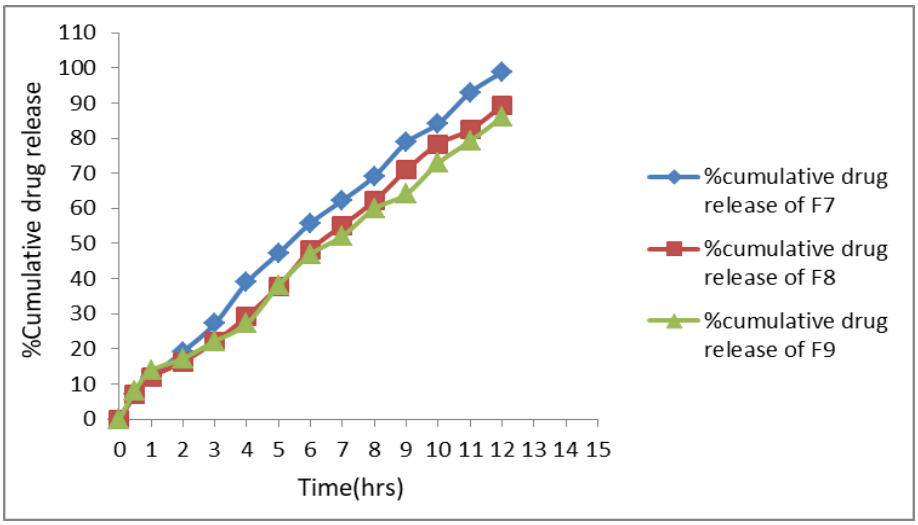

Fig: Dissolution profile of Terbutaline sulfate (F7, F8, F9 formulations)

CONCLUSION

The aim of the present study was to develop controlled release buccal formulation of Terbutaline Sulfate to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC K 4M, HPMC K 15M, HPMC K 100M were employed as polymers. Terbutaline Sulfate dose was fixed as 2.5 mg. Total weight of the tablet was considered as 60 mg. Polymers were used in the concentration of 5mg, 7.5mg and 10mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F7) showed better and desired drug release pattern i.e.,98.76 % in 12 hours. It followed zero order release kinetics mechanism.

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