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FORMULATION & EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF METOPROLOL SUCCINATE

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ABSTRCT

In this study Metoprolol Succinate buccal tablets were prepared and optimized the release of Metoprolol Succinate by using Carbopol, Sodium alginate and Sodium carboxy methyl cellulose as polymers. The tablets prepared by direct compression technique and evaluated by physical parameters and invitro dissolution parameters. A total nine formulations were prepared with varying polymer concentrations. All tablets were acceptable with strength was observed in tablets formulated with Carbopol, sodium alginate and Sodium carboxy methyl cellulose. Formulation F9 showed maximum release 99% in 8 hrs. FT-IR studies showed no evidence of interaction between drug and polymers.

KEYWORDS: *Metoprolol Succinate buccal tablets, Carbopol, sodium alginate and Sodium carboxy methyl cellulose.*

INTRODUCTION

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectable as carriers. Amongst various routes of drug delivery oral route is perhaps the most preferred to the patient and the clinician alike. However this route presents some problems for a few drugs. The enzymes in the GI fluids, GIT-pH conditions and the enzymes bound to GIT membranes are a few factors responsible for the bioavailability problems. The blood that

drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability. The inherent problems associated with the drug in some cases can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs.

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. Extensive first-pass metabolism and drug degradation in the harsh GI environment can be circumvented by administering the drug via buccal route. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration. Drug absorption through buccal mucosa is mainly by passive diffusion into the lipoidal membrane. After absorption the drug is transported through facial vein which then drains into the general circulation via jugular vein bypassing the liver and thereby sparing the drug from first-pass metabolism. Buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides as well as conventional small drug molecules. The oral cavity can be used for local and systemic therapy.

Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism or for the administration of proteins and peptides.[1,2]

Drug delivery via buccal route[3,4]

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated of the following.

Advantages of Buccal Drug Delivery Systems

Drug administration via buccal mucosa offers several distinct advantages,

1. Ease of administration.

2. Permits localization of the drug in the oral cavity for a prolonged period of time.
3. Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
4. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
5. Drugs which are unstable in acidic environment of the stomach are destroyed by the enzymatic or alkaline environment of the intestine.
6. The presence of saliva ensures relatively large amount of water for drug dissolution unlike the case of rectal and transdermal routes.
7. It offers passive system for drug absorption and does not require any activation.
8. It can be made unidirectional to ensure only buccal absorption.

Disadvantages of buccal drug delivery system

Drug administration via buccal mucosa has certain limitations,

1. Drugs which irritate the oral mucosa have a bitter or unpleasant taste or odour cannot be administered by this route.
2. Drugs, which are unstable at buccal pH, cannot be administered by this route.
3. Only drugs with small dose requirements can be administered.
4. Drugs may get swallowed with saliva and loses the advantages of buccal route.
5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
6. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.
7. The buccal mucosa is relatively less permeable than the small intestine, rectum, etc.

Conventional Dosage Form

The conventional type of buccal dosage forms are buccal tablets, troches and lozenges and mouth washers. Buccal tablets are small, flat, oval tablets and are intended to be held between the cheek and the teeth or in the cheek pouch (buccal tablets). Progesterone tablets can be administered this way. Troches and lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat. These tablet forms are commonly used to treat sore throat or to control coughing in common cold. Lozenges (pastilles or cough drops) are usually made with the drug incorporated in a flavored, hard-

candy sugar base. Lozenges may be made by compression but are usually formed by fusion or by a candy – moulding process. Troches, on the other hand, are manufactured by compression as are other tablets. These two classes of tablets are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps minute or less.

MUCOADHESION[11-13]

Definition

The term bioadhesion is defined as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface. The general definition of adherence of a polymeric material to biological surfaces (bioadhesive) or to the mucosal tissue (mucoadhesive) still holds. A bioadhesive has been defined as a synthetic or biological material which is capable of adhering to a biological substrate or tissue and when the biological substrate is mucus the term was known as mucoadhesive.

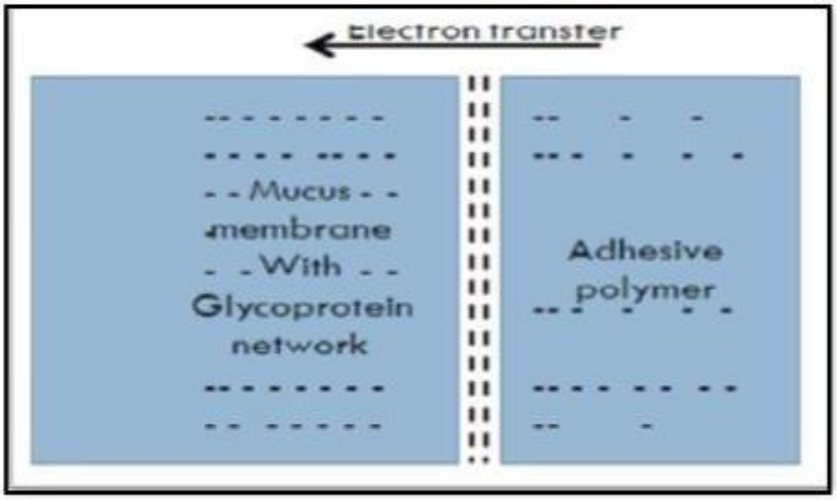
Theories of mucoadhesion

There are five theories explain the processes of Mucoadhesion which are given as, electronic theory, absorption theory, wetting theory, diffusion theory and fracture theory.

The electronic theory

This theory is based on the assumption that the bioadhesive material and the glycoprotein mucin network have different electronic structures. When the two materials come in contact with each other electron transfer will occur causing the formation of a double layer of electrical charge at the interface. The bioadhesive force is due to attractive forces across this electrical double layer. The system is charged when the adhesive and the substrate are in contact and discharged when they are separated. However, this theory has caused some controversy regarding whether the electrostatic forces are an important cause or the result of the contact between the bioadhesive and the biological tissue.

Electronic theory



The absorption theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished:

I) Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds.

II) Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander walls forces and hydrogen and hydrophobic bonds.

The wetting theory

According to this theory the ability of bioadhesive polymer or mucus to spread and develop intimate contact with their corresponding substrate or bond formation. The contact angle (θ) which

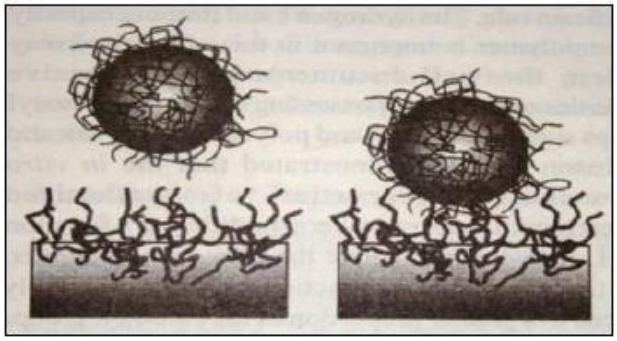
$$\lambda t_g = \lambda b_t + \lambda b_g \cos\phi$$

should be zero or near zero for proper spreading is related to interfacial tensions (γ) through young's equations, Where the t, g and b stand for tissue, gastro intestinal contents and bioadhesive polymers respectively must equal to zero for spontaneous wetting to occur. Using wetting theory, it is possible to calculate spreading coefficients for various bioadhesive over biological tissues and predict the intensity of the bioadhesive bond. Hence, it provides essential information for development of bio-adhesive drug delivery system.

Diffusion theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanat adhesive bond. The exact depth to which the polymer chains penetrate the

mucus depends on the diffusion coefficient and the time of contact. This diffusion co efficient, in turn, depends on the value of molecular weight between crosslink's and decreases significantly as the cross linking density increases. This theory suggests that interpenetration and entanglements of bio-adhesive polymer chain and mucus polymer chains produce semi permanent adhesive bonds, and bond strength is believed to increase with the depth of penetration of the polymer chains.



Diffusion theory

Fracture theory

This theory analyses the force that is required to separate two surfaces after adhesion. The maximum tensile stress (μ) produced during detachment can be determined by dividing the maximum force of detachment, F_m by the total surface area (A_0) involved in the adhesive interaction.

$$\sigma_m = F_m / A_o$$

The above equation can be used for calculating fracture strengths of adhesive bonds involving hard, bioadhesive material in which the polymer chains may not penetrate the mucus layer.

MATERIALS AND METHODS

Table No.06: FORMULA.

Ingredients (mg per tablet)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Metoprolol Succinate	10	10	10	10	10	10	10	10	10
Carbopol	15	35	40	20	45	20	35	30	40
sodium alginate	30	10	35	20	20	45	30	30	20
Sodium carboxy methyl cellulose	40	40	10	45	20	20	20	25	35
magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Citric acid	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total tablet weight	100	100	100	100	100	100	100	100	100

FORMULATION

All the ingredients sufficient for a batch of 20 tablets according to formula was passed through sieve in order to enhance the flow and compaction properties and drug was triturated with polymer in a glass mortar and pestle to achieve a homogenous blend and geometrically mixing was done with effervescent agent, filler and other excipients sufficient for a batch of 20 tablets according to the formulae were passed through the mesh and thoroughly the blend was mixed with lubricant ensure complete mixing. Tablets (100mg) were compressed by using 10.0mm diameter, spherical tablet punches on a 16 station rotary compression machine at the hardness of 4 to 6 kg/cm.[2]

EVALUATION OF FORMULATION BLEND

Angle of repose

The flow property was determined by measuring the angle of repose. In order to determine the flow property, the angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane. Values of are rarely less than 20^0, and values of up to 40^0 indicate reasonable flow potential. Above 50^0, however, the powder flows only with difficulty if at all.

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

Where

h = height the pile

r = radius of the pile

 = angle of repose

The sample was taken in a funnel, which fixed in a holder (5cm) above the surface at an appropriate height and a graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Bulk Density and Tapped Density

The powder (W) was carefully poured into the graduated measuring cylinder and the volume (VO) was measured. Then the graduated cylinder was closed with lid and tapped 100times and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the

following formulas

$$\text{Bulk density} = W / V_O \quad \text{Tapped density} = W / V_f$$

Where,

W = weight of the powder

V_O = initial volume

V_f = final volume

Compressibility Index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$CI = 100 \frac{(V_O - V_f)}{V_0}$$

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Formula: Hausner's Ratio = Tapped density/Bulk densit

Drug- Excipients compatibility studies

API and Excipients are mixed in different ratios and mixed together in a poly bag for 5 mins. Each mixture is allotted sample code for identification and mixtures are thoroughly sealed in a glass vials and exposed to different temp and humidity conditions.

The samples are to be checked for its descriptions, related substance and water content by KF. The prepared drug and exipient mixture were evaluated at various intervals for related substances by HPLC as per the following conditions and time intervals.

EVALUATION OF COMPRESSED TABLETS[33-36]

Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is

usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets have a hardness of 3 kg and some sustained release tablets have a hardness of 10 - 20 kg.

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier caliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where, I - Initial weight

F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

Percentage deviation = [X-*X/ X] × 100 X -** Actual weight of the tablet

X*- Average weight of the tablet

Weight variation Tolerances for uncoated Tablets

Estimation of Drug Content

An accurately weighed amount of powdered drug (100 mg) was extracted with water and the solution was filtered through 0.45 µ membrane filter paper. The absorbance was measured at 275 nm after suitable dilution.

CALCULATION

The amount of drug present in tablet can be calculated using the formula

$$A_t/A_s \times S_w/100 \times 100$$

Where,

A_t = Absorbance of sample preparation

A_S = Absorbance of Standard preparation

S_W = weight at Metformin working standard (mg)

Dissolution test

In vitro dissolution test was carried out by using USP type II (paddle) apparatus. 1000 mL of acetate buffer pH 4 with 1% triton X-100 was used as dissolution medium and the paddle was rotated at 60 rpm at temperature (37^0C ± 0.5^0C). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analysed spectrophotometrically at λmax of the drug.

Medium**:**	buffer pH 1.2
Volume:	1000mL
Temperature:	37^0C±0.5^0C
Apparatus:	USP type-II (paddle)
RPM:	50 RPM
Time interval:	1 hr up to 12 hrs

***Invitro* Drug Release Studies**[37-39]

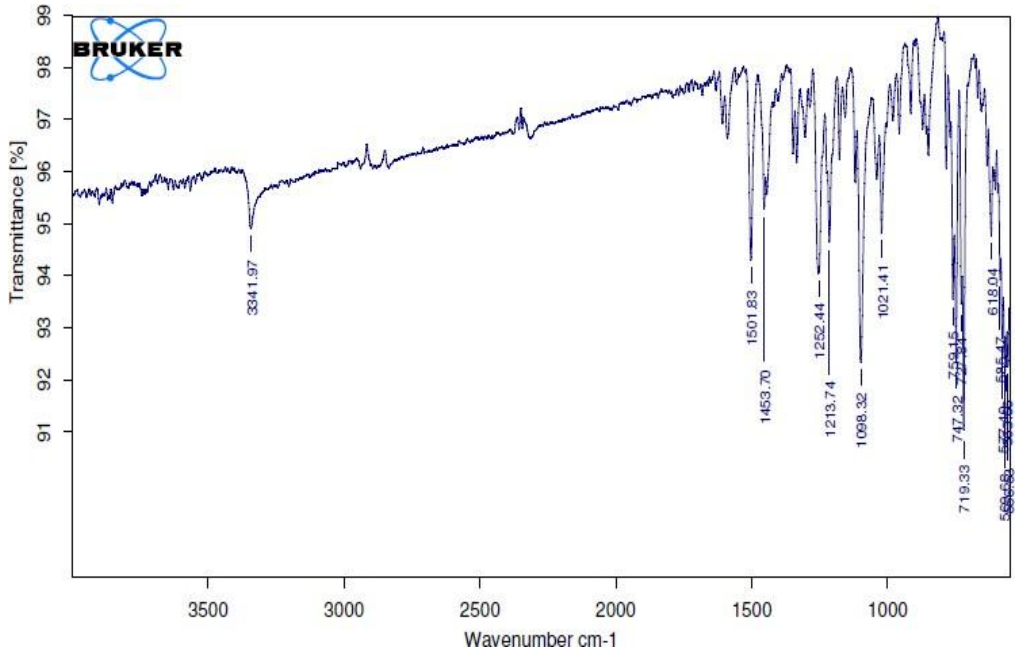
Invitro drug release from the hydrogels were carried out in triplicate at 37°C±0.1°C in a USP type II rotating basket dissolution apparatus at a rotation speed of 50rpm. Drug release from the hydrogels were studied both in 900ml of in pH1.2 buffer for 12hours. At regular time intervals i.e., at every one hour, samples were withdrawn and analyzed for the drug using a UV visible spectrophotometer. Drug release from the buccal tablets was also studied separately in both 900ml of 1.2 pH buffer. The release data obtained were fitted into various mathematical models to know which mathematical model was best to fit the obtained release profile. The parameters; the time exponent (n), the release rate constant (k), the regression coefficient (R^2), were determined for Korsmeyer-Peppas equation to know the release mechanism. The various models studied were

1. Zero order
2. First order
3. Higuchi model
4. Peppas model

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows,

1. Cumulative% of drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining to be absorbed versus time (First order model)
3. Amount of drug release or cumulative amount of drug release versus square root of time (Higuchi model)
4. Log Mt/M ∞ versus log time(Peppas model)

RESULTS AND DISCUSSIONS

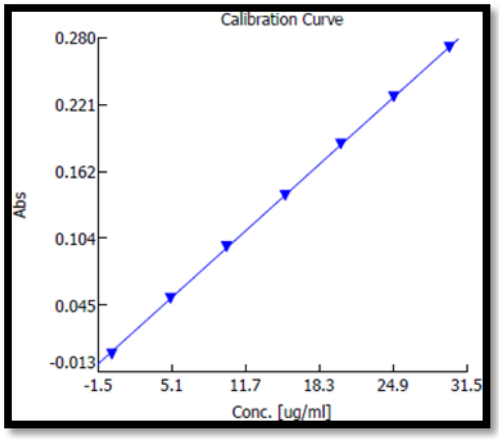


FT- IR Studies.

CONSTRUCTION OF STANDARD GRAPH OF METOPROLOL SUCCINATE

Standard curve of Metoprolol Succinate.

Concentration (µg/ml)	Absorbance at 238 nm
0	0
5	0.065
10	0.089
15	0.128
20	0.200
25	0.228
30	0.266



Standard curve of Metoprolol Succinate R^2: 0.9934

EVALUATION OF PREPARED BUCCAL TABLETS

All the prepared tablets were evaluated and the results are as following.

Precompression studies

13 Results of flow properties

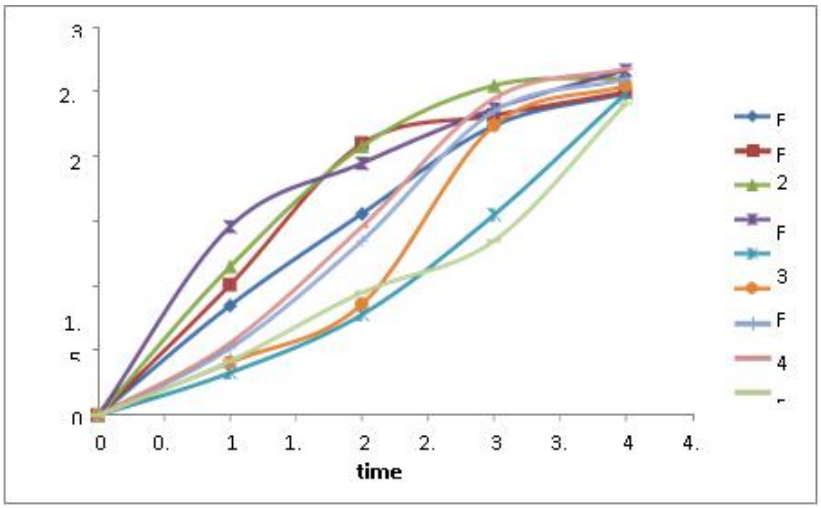
S.No	Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (I)	Hausner's ratio
1	F1	24.16	0.512	0.647	10.84	1.28
2	F2	23.74	0.549	0.673	12.42	1.25
3	F3	24.70	0.532	0.650	11.15	1.23
4	F4	26.65	0.545	0.651	11.28	1.20
5	F5	24.69	0.541	0.655	12.40	1.21
6	F6	23.89	0.535	0.668	12.91	1.25
7	F7	29.01	0.541	0.682	10.67	1.24
8	F8	29.72	0.532	0.670	12.59	1.25
9	F9	27.54	0.529	0.665	10.45	1.18

Post compression studies

Results of Post compression Studies

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0.85	1.01	1.15	1.46	0.33	0.41	0.52	0.56	0.42
2	1.56	2.1	2.08	1.95	0.78	0.86	1.35	1.46	0.95
3	2.24	2.32	2.55	2.37	1.55	2.24	2.35	2.45	1.35
4	2.49	2.5	2.61	2.67	2.49	2.55	2.60	2.68	2.41

Swelling index profile of formulation

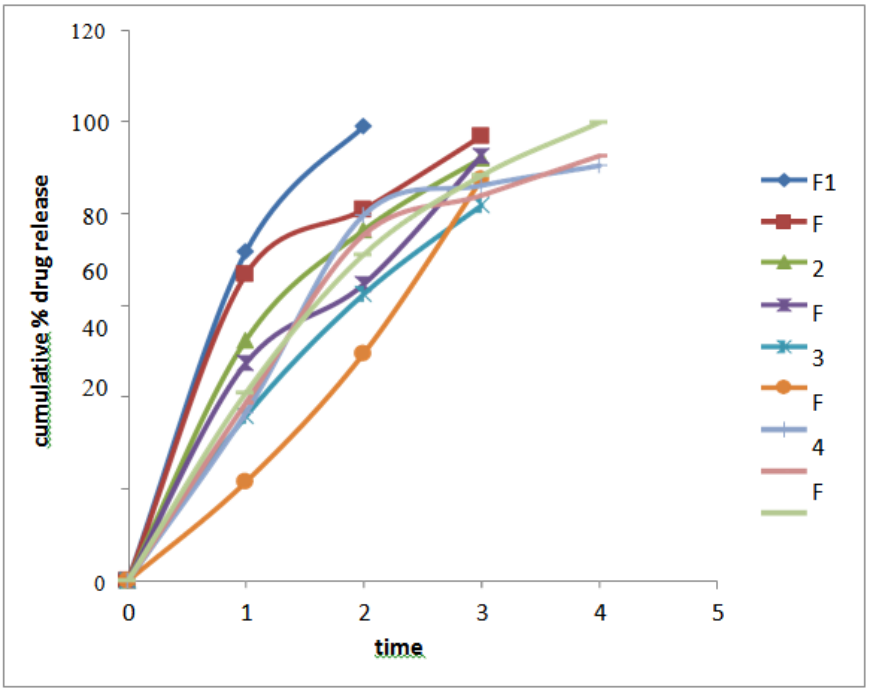


Swelling index profile of formulations

***In-vitro* cumulative percentage drug release**

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	71.71	66.79	52.45	47.40	35.85	21.54	36.63	38.78	40.94
2	99.11	80.96	76.43	64.64	62.48	49.55	79.72	75.41	71.10
3		96.96	92.14	92.65	81.88	87.55	86.19	84.03	88.34
4							90.5	92.65	99.91

***In vitro* cumulative percentage drug release profile**



SUMMARY AND CONCLUSION

Metoprolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, Metoprolol Succinateis preferentially β1 selective. In poor metabolizers and at higher doses, Metoprolol Succinateinhibits both β1 - and β2 - adrenergic receptors. Metoprolol Succinatelacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations.

In the present study different polymers like carbopol, sodium alginate and Sodium carboxy methyl cellulose were used to prepare Metoprolol Succinatebuccal tablets. Drug and polymers were subjected for compatibility study using differential scanning calorimetry, which suggested that there was no interaction between drug and polymers. To analyze the mechanism of drug release from the tablets, the invitro permeation data were fitted to zero order, first order, Higuchi release model and Korsmeyer and Peppas model.

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The drug and polymers were subjected for the compatibility study using DSC, which suggested that there was no significant interaction between the drug and polymers.

This study suggests that formulation 9 (F9) shows the optimized release in all aspects. The optimized formulation shows required physical and formulation parameters. By using the formulation we can deliver the Metoprolol Succinate drug in optimized manner.

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