Indian Journal of Research in Pharmacy and Biotechnology
Volume 6, Issue 3, 2018
Journal homepage: http://www.ijrpb.com

ISSN:
2321-5674 (Print)
2320-3471
(Online)

Research article

Indexed in CAS and CABI
Impact factor:0.64

Design and development of buccal tablets of Metoprolol tartarate by core in cup technology

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Keywords:
Metaprolol tartarate, Mucoadhesive, Buccal drug delivery.

Article Info:
Received: 19-04-2018
Revised: 28-04-2018
Accepted: 15-05-2018

ABSTRACT

A precise, simple, cost effective, accurate Ultra violet spectrophotometric method has been developed for the determination of Edoxaban Tosylate Monohydrate (EDTM) in the Pharmaceutical dosage form. EDTM shows highest λmax at 291.2 nm. The EDTM follows linearity in the concentration range of 2-10 µg /mL with superior correlation coefficient value of 0.999. The precision of the method was studied as an intra-day and inter-day studies. The % RSD value is < 2 which indicates that the method is precise. The % recovery was found to be in the range lies between 99.75 - 99.85 %. Percentage assay of EDTM (Lxiana) obtained was 98.5 ± 1.85 %. The Proposed spectrophotometric method was validated as per the ICH Q2 (R1) guidelines. The proposed UV method is accurate, precise and reproducible. Hence this rapid method can be viable for the quality control analysis of EDTM in pharmaceutical dosage form.

1. INTRODUCTION

The aim of study is to develop the mucoadhesive buccal tablets of metaprolol tartarate by core in cup technology. Mucoadhesive drug delivery system is a drug delivery system which utilise the property of bioadhesion attachment of a drug carrier system to a specific biological surface (epithelial tissuse;for drug delivery process).Bioadhesion is an interfacial phenomenon in which two materials at least one which is biological re held together by means of interfacial forces. It adhesive attachment is to a mucin layer that phenomenon is termed as 'mucoadhesion'. In mucoadhesion the mucin layer as biological substrate and the material which attaches to the mucin layer is polymer.[1,2]

Theory of mucoadhesion: Various theories exist to explain at least some of the experimental observations made during the bioadhesion process among them mucoadhesive buccal tablets of metoprolol tartarate follows diffusion theory.

Diffusion theory of mucoadhesion: In this theory, the physical entanglement of glycoprotein strands into the versatile chemical compound chains are associate in nursing interpenetration of glycoprotein strands into porous structure of the chemical compound substrate ends up in mucoadhesion.[3]

Steps of mucoadhesion: There are steps involved in mucoadhesion process. They are contact stage and consolidation stage. The first stage or the contact stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating is deep contact with mucus layer.in the consolidation stage, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to cleave free and to link up by weak Vander Waal's and hydrogen bonds.

Mechanism of mucoadhesion:

Mucoadhesion is mainly based on molecular interactions. The interaction between two molecules is composed of attraction and repulsion. Attractive interactions include Vander Waal's forces, electrostatic attractions, hydrogen bonding and hydrophobic interactions. Repulsive interactions include electrostatic and steric repulsion. For mucoadhesion to occur, the attractive interaction should be more than non-specific repulsion[6-8]. This process of Mucoadhesive bond formation has been described by three stages:

Stage 1: Wetting and swelling of polymer to permit intimate contact with biological tissue.

Stage 2: Interpretation of bioadhesive polymer chains and entanglement of polymer and mucin chains.

Stage 3: Formation of chemical bonds between the entangled chains.

Formulation of buccal drug delivery system:

Formulation design:

a. General criteria for selection of drug candidate

b. Pharmaceutical considerations

c. Buccal adhesive polymers

Advantages of mucoadhesive buccal delivery system:

- Significant reduction in dose related side effects.
- It provides direct entry of drug into systemic circulation.
- Drug degradation in harsh gastrointestinal environment can be circumvented by administering the drug via buccal route.
- Drug absorption can be terminated in case of emergency.
- It offers passive system, which does not require activation.
- Rapid cellular recovery following local stress or damage.

Limitations of mucoadhesive buccal drug delivery system:

- Drugs which irritate oral mucous membrane or have bitter taste, or cause allergic reactions, discoloration of teeth cannot be developed.
- If formulation contains antimicrobial agents, affects the natural microbes with in the buccal cavity.
- The patient cannot eat/drink/speak.

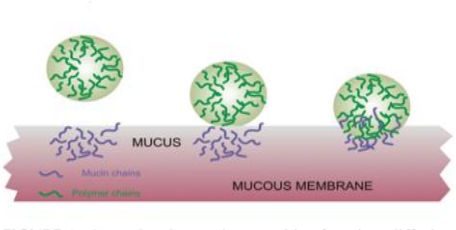

Figure.1.Diffusion theory of mucoadhesion

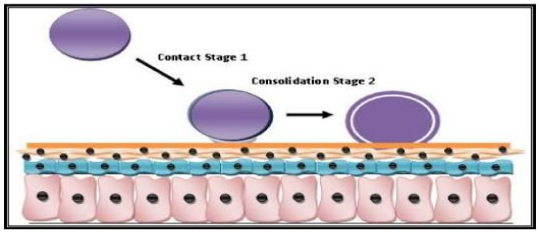

Figure.2.The two steps of mucoadhesion process

2. MATERIALS AND METHODS

Metoprolol tartarate was kindly donated by Aurabindo pharma, Hyderabad. Polymers like Ethyl cellulose, cellulose acetate, carbopol 934, Hydroxy Propyl methyl cellulose (Non-ionic polymer), Methyl cellulose, Sodium carboxy methyl cellulose are purchased from universal laboratories. Other chemicals and other excipients used in the formulation are purchased from CDH, Hyderabad.

Buccal tablets of metoprolol tartrate by core in cup technology. Core tablet was prepared by wet granulation technique by using various polymers like ethyl cellulose and cellulose acetate as bioadhesive polymers and lactose as diluents. The blend was subjected to sieving method in sieve # 12. Granules are dried in tray dryer for 20 minutes. Then they are lubricated with magnesium stearate for 3-5 minutes and talc was added as glidant. The mixed blend was compressed into tablets by direct compression method using 9mm flat punches in a rotary tablet punching machine. Each tablet contains 50 mg of metoprolol tartrate. The mass of the tablet was determined by digital balance (Shimadzu) and thickness with Vernier calipers.

Figure.3. Powder blend of tablet

Figure .4. Dried granules

Figure.5. Core tablet

Figure.6. Core tablets

The cup tablet was prepared by using polymers HPMC, MC, Carbopol 934, Na CMC by 16 station rotatory compression machine by using special punch and lubricated to prepare core in cup tablets, newly designed upper 12 mm punch and lower punch remains flat faced. The core tablet was placed in cup tablet using acrycat l-30 DA gum. The core in cup tablets are coated with film which is made up of 500 mg of CAP and 5 ml of Ethanol and 5 ml of Acetone after dissolving add 2 drops of N-di butyl phthalate. Viscous solution appears which is coated as film on core in cup tablets and dried naturally.

Table.1.Formulation of core tablet

Materials	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
Metoprolol tartrate	50	50	50	50	50	50
Cross povidone	10	10	10	10	10	10
Ethyl cellulose	25	50	75	-	-	-
Cellulose acetate	-	-	-	25	50	75
Lactose	111	86	61	111	86	61
Mg stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total	200	200	200	200	200	200

Table.2.Formulation for cup tablet

Materials	Trail-1	Trail-2	Trail-3	Trail-4
Na CMC	400 mg	-	-	-
HPMC	-	400 mg	-	-
Carbopol	-	-	400 mg	-
MC	-	-	-	400 mg
MCC	42 mg	42 mg	42 mg	42 mg
Mg stearate	4 mg	4 mg	4 mg	4 mg
Talc	4 mg	4 mg	4 mg	4 mg
Total	450 mg	450 mg	450 mg	450 mg

Evaluation tests: The λ max of Metoprolol tartarate was observed by carrying out UV scan between the wavelength 200-400 nm which gives the highest peak at 221 nm. Other pre compressional evaluation parameters like bulk density, tapped density, compressibility index, Angle of repose, Hausners ratio. The post formulation evaluation studies are weight variation test, Thickness, Hardness and friability test are performed

Drug Content (% Assay): To determine the drug content three tablets from each formulation were weighed individually, crushed and diluted to 100ml with sufficient amount of purified water. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 225.5 nm against blank. The drug content of each formulation was evaluated as per the standard protocol ranges between 99-101%w/v.

3. RESULTS AND DISCUSSION

Table.3. Interpretation values of Metaprolol tartarate

Group	Range (cm^{-1})
O-H stretching	3550-3200
Methyl	2933.78
C-O-C	1300-1000
2^0 amines	3310-3140

Table.4.Interpretation values of Drug + Ethyl cellulose

Group	Range cm^{-1}
O-H stretching	3478.65
Polymer	3906.82
Carboxy group	1743.72
C-O-C	1113.51

Table.5.Interpretation values of Drug +Cellulose acetate

Group	Range cm^{-1}
O-H Streching	3478.9
C-H Streching alkane	2976.78
Polymer	3906.82
Carboxy	1743.72
Amines weak absorption	1609.7

Pre formulation evaluation studies:

Table.6.Pre compression evaluation data for tablet powder blend

Batch no	Bulk density	Tapped density	Carr's index	Hauser's Ratio	Angle of repose
Batch 1	0.401±0.003	0.490±0.004	8.32	1.22	25'23

Table.7.Pre compression evaluation data for core tablets

Parameters	Bulk density	Tapped density	Carr's index	Hauser's ratio	Angle of repose
F1	0.579±0.003	0.698±0.003	14.63	1.17	27'33◦
F2	0.587±0.004	0.665±0.006	16.77	1.20	26'41◦
F3	0.479±0.005	0.548±0.035	16.51	1.19	28'22◦
F4	0.567±0.004	0.626±0.001	13.84	1.16	26'44◦
F5	0.573±0.004	0.641±0.002	14.52	1.17	27'10◦
F6	0.581±0.001	0.621±0.003	16.83	1.18	26'98◦

Post formulation evaluation data for core tablets:
F3 Core tablet shows better properties than other core tablets, so F3 was selected to insert in cup formulation and to perform further evaluation tests.

Table.8. Post compression evaluation data for core tablets

Parameters	F1	F2	F3	F4	F5	F6
Weight variation(mg)	198±0.69	198±0.22	199.96±0.20	189.1±0..71	198.9±0.11	199±31
Thickness(mm)	3.34±0.12	3.04±0.23	2.91±0.26	2.99±0.78	3.35±0.88	3.12±0.23
Diameter(mm)	8.16±0.23	8.23±1.32	8.03±0.017	7.01±0.18	7.12±0.034	9.01±0.12
Hardness($kgcm^2$)	10.0±0.12	9.09±0.34	4.36±0.057	9.34±0.067	8.99±0.212	9.01±0.122
Friability (%)	0.392±0.28	0.421±0.11	0.318±0.025	0.381±0.012	0.521±0.23	0.333±0.122
Drug content (%)	99.4±0.72	98.02±0.34	99.42±0.831	99±0.55	97.9±0.99	98.2±0.12
Disintegration time	35.02±0.44	34.56±0.37	20.6±0.577	34.52±0.78	25.09±0.19	29.6±0.81

Table.9. Evaluation Results for F3 core tablet

Parameters	F3
Weight variation (mg)	69.96±0.20
Thickness (mm)	2.91±0.26
Diameter (mm)	8.03±0.017
Hardness (kg/cm^2)	4.36±0.057
Friability (%)	0.318±0.025
Drug content (%)	99.42±0.831
Disintegration time (sec)	20.6±0.577

In-vitro drug release study: In vitro dissolution of designed core tablet and core in cup tablets were studied using USP Apparatus 2 paddle method. The dissolution profile dissolution data and model fitting values were presented in tables

Table.10.In-vitro Dissolution data of core tablet

S.No	Time (min)	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	5	0.12	0.14	6.56	0.28	0.13	0.10
3	15	28.54	0.20	12.54	12.56	2.17	0.95
4	30	50.34	5.43	15.68	28.18	32.95	18.50
5	60	96.37	35.68	40.34	54.56	69.12	30.34
6	120	96.37	56.32	56.56	60.30	95.23	52.12
7	180	96.37	93.62	62.12	85.17	-	75.34
8	240	96.37	93.62	98.37	90.52	-	88.66

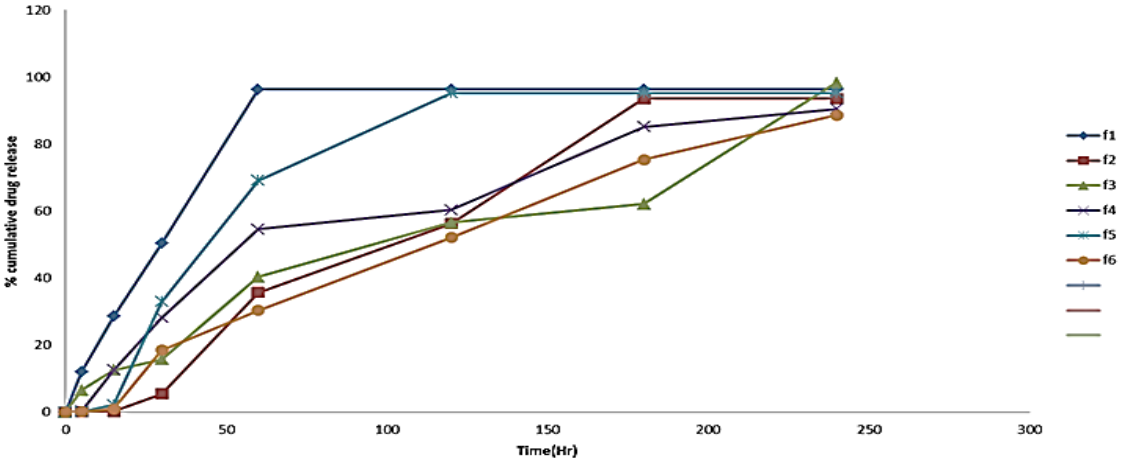

Figure.12.Comparative graph for In-vitro dissolution studies of core tablets

Table.11.In-vitro evaluation for core in cup formulation by using various polymers

Time (hours)	Trial 1	Trial 2	Trial 3	Trial 4
0	0	0	0	0
1	0	1.05	0	1
2	21.63	20.15	12.99	19.8
4	42.56	39.8	32.89	40.2
6	65.44	62.48	55.69	65.4
8	86.91	70.98	68.42	75.4
10	99.53	96.54	92.6	90.2

Table.12. Regression coefficient values for core in cup formulations

Regression Coefficient Values	T1	T2	T3	T4
Zero Order Kinetics	0.985	0.984	0.990	0.978
First Order Kinetics	0.742	0.746	0.799	0.709
Higuchis	0.940	0.906	0.880	0.917
Peppas	0.900	0.901	0.941	0.901
Diffusion Coefficient	0.202	0.197	0.201	0.198

Figure.13. Zero order plot for core in cup tablets

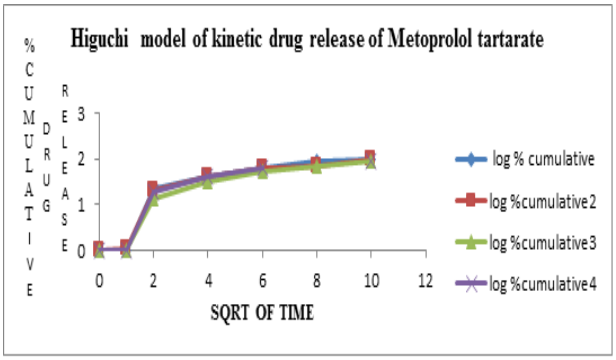

Figure.14.Higuchi plot for core in cup tablets

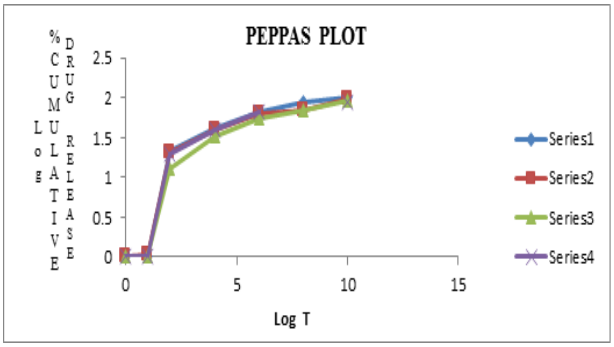

Figure.15. Peppas plot for core in cup tablets

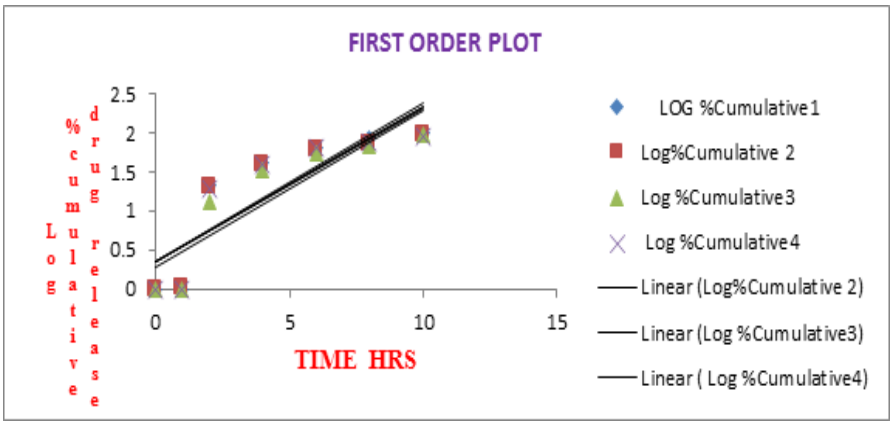

Figure.16.First order plot for core in cup tablet

4. CONCLUSION

Drug excipient interaction studies (FTIR) OF metoprolol tartrate with different excipients were done. By interpretation of IR spectrum of metoprolol tartrate with that different excipients has declared that there is no incompatibility between drug and excipients. Core tablets of metoprolol tartrate formulated by using two different polymers such as cellulose acetate and ethyl cellulose with various excipients as shown in table no.1. Pre compression evaluation tests like bulk density, tapped density, angle of repose, compressibility index, Hauser's ratio were done by observing results we had declared that F3 formulation core tablet of metoprolol tartrate has shown better results when compared to other five formulations (F1,F2,F4,F5,F6).The results for F3 formulations are bulk density (0.479±0.005), Tapped density (0.548±0.035), Carr's index(16.51), Hauser's ratio (1.19),Angle of repose (28'22◦) which were mentioned in table no:13.Post compressional parameters like Weight variation (199.96±0.20 mg),Thickness (2.91±0.26 mm), Diameter (8.03±0.017 mm), Hardness (4.36±0.057 kg $cm^{2)}$, Friability (0.318±0.025 %), Drug content (99.42±0.831%), Disintegration time(20.6±0.577) was mentioned in table no: 14 and In-vitro drug dissolution data for F3 was mentioned in table no: 16.F3 tablet was placed in cup using various polymers. Finally, we concluded that the formulation made with carbopol 934 is taken as best formulation than other formulations.

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