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Evaluation of Oral Mucoadhesive Metoprolol succinate Controlled Release Tablets

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Review Article

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ABSTRACT

The idea of mucoadhesive was derived from the requirement to localize medication at a particular site within the body. Extent of drug absorption are often increased by increasing duration of the drug at the absorption site within the GI tract. Since several medication are absorbed solely from the higher a part of the bowel localizing oral drug delivery systems within the abdomen or within the small intestine would considerably improve the extent of drug absorption

The idea of mucoadhesive was derived from the requirement to localize medication at a particular site within the body. Extent of drug absorption is often increased by increasing duration of the drug at the absorption site within the GI tract. Since several medication are absorbed solely from the higher a part of the bowel localizing oral drug delivery systems within the abdomen or within the small intestine would considerably improve the extent of drug absorption

Review Article

Oral controlled free dose forms are gradully developing over the past 3 decades, as a result of the therapeutic applications such as ease of administration, patient compliance, and adaptability in formulation. But this approach deals with many physiological difficulties like inability to resist and find the management the delivery of the drug inside the desired reason of the gastro-intestinal tract due to variable stomach remotion and motility.

The flexibility to of the delivery system to a specific location for an extended amount of your time includes a nice charm for each native unwellness treatment also as general drug bioavailability [1-9].
Drug formulations that have bioadhesive properties will prolong the duration for the drug at the positioning of absorption, the possibly up membrane transport. The flexibility to extend bioadhesion would be particularly vital for active compounds that square measure poorly soluble and permeates poorly.
Oral drug delivery has been known for many centuries as the most widely easy route of administration among all routes that have been explored for systemic delivery of drugs in case of different dosage forms [10-18].

The scientific framework required for the successful development of an oral drug delivery system consists of basic understandings of following aspects:
1. Physicochemical, Pharmacokinetic and Pharmacodynamic characteristics of drugs.
2. Anatomical and biological and physiological characteristics of gastrointestinal digestive system.
3. Physiomechanical characteristics and drug delivery mode of a dosage from to be designed [19-24].

Mucoadhesive drug delivery system offer intimate contact between indefinite quantity form and also the tissue, which can end in high-localized drug concentration and hence high drug flux across the tissue.The intimate contact is probably going to extend the overall permeableness of high mass medication like peptides and proteins. By incorporating a permeation foil, drug absorption through membrane are often increased and so will increase the bioavailability of the drug [25-29].

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Oral controlled have indefinite quantity forms are developed over the past 3 decades owing to their substantial therapeutic activity like simple administration, patient compliance and adaptability in formulation. However, this approach is bedilled with many physiological difficulties like inability to restrain and find the controlled drug delivery system inside the required region of the channel (GIT) owing to variable stomachal evacuation and motility. moreover, the comparatively temporary stomachal evacuation time (GET) in humans that unremarkably averages 2-3 hrs through the key absorption zone, i.e., abdomen and higher a part of the internal organ may end up in incomplete drug unleash from the drug delivery system resulting in reduced effectiveness of the administered dose. Therefore, management of placement of a drug delivery system during a specific region of the alimentary tract offers medicine characterised by a slender absorption window within the medicine with a stability drawback [30-37]. These concerns helped to the event of a novel oral controlled indefinite controlled release with gastroretentive properties. When oral administration, such as dosage forms would be preserved within the abdomen and release the drug there during a controlled and prolonged manner, in order that the drug may be equipped endlessly to its absorption sites within the higher channel. Gastroretentive indefinite quantity type will stay within the stomachal region for many hours and thus considerably prolong the stomachal continuance of medicine. Prolonged stomachal retention improves bioavailability, reduces drug waste [38-45].

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION

In general, appropriate candidates for Controlled release Gastro are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa
2. Primarily absorbed from stomach and upper part of GItract, e.g., calcium supplements, chlordiazepoxide and cinnarazine [46-54].
3. Drugs that act locally in the stomach, e.g., antacids and misoprostol
4. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole
5. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

INFORMATION ON DRUG PROFILES OF METOPROLAL SUCCINATE

Metoprolol may be a selective β1 receptor blocker employed in treatment of many diseases of the circulatory system, particularly high blood pressure. The active substance beta-adrenergic blocking agent is used either as beta-adrenergic blocking agent succinate or beta-adrenergic blocking agent salt severally as prolonged-release or conventional-release formulation.

Chemical name: (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt).

Pharmacokinetics [55-59]:

Absorption: beta-adrenergic blocking agent is well absorbed when oral administration, peak plasma concentrations occurring one.5 - a pair of hours when dosing.
Bioavailability: The bioavailability is twelve-tone music.

Distribution*:* About 100% of beta-adrenergic blocking agent in plasma is macromolecule certain. beta-adrenergic blocking agent crosses the placenta.

Metabolism: Beta-adrenergic blocking agent is extensively metabolized by enzymes of the haemoprotein P450 system within the liver. The aerophilous metabolism of beta-adrenergic blocking agent is below genetic management with a serious contribution of the polymorphic haemoprotein P450 isoform 2D6 (CYP2D6) [60-67].

Half life: 3-7 hours.

Mechanism of Action: It's a comparatively larger interference result on beta1-receptors (i.e. those mediating adrenergic stimulation of rate and ability and unharness of free fatty acids from fat stores) than on beta2-receptors that square measure mainly concerned in bronco and vasodilatation. it's neither membrane-stabilising result nor

partial agonist (intrinsic sympathomimetic) activity.The stimulant result of catecholamines on the guts is reduced or repressed by beta-adrenergic blocking agent. This results in a decreaseS in rate, viscus ability and rate of flow [68-75].

Indications of use:

1. high blood pressure,
2. heart disease,
3. Heart failure- for the treatment of stable, symptomatic
4. Heart disease of anaemia, hypertensive, or cardiomyopathicccs origin.

INFORMATION ON EXCIPIENT PROFILES OF HYDROXY PROPYL METHYL CELLULOSE 15 [76-84]

1. Non-proprietary names: Bp: Hypromellose
2. USP: Hydroxy propyl methyl cellulose
3. Synonyms: Methyl hydroxy propyl cellulose, propylene glycol either of methylcellulose,methylcellulose, methylcellulose propylene glycol ether.
4. Chemical name: Cellulose, 2-hydroxypropyl-methyl ether
5. Empirical formula: C8H15O6 – (C10H18O6) n – C8H15O5
6. Description: It occurs as odorless and tasteless creamy white colored fibrous or glandular powder.
7. Functional category: Coating agent, film former, tablet binder, stabilizing agent, suspending agent, viscosity increasing agent.
8. Density: 0.25 – 0.70 g/cm^3
9. Solubility: Soluble in cold water forming viscous colloidal solution, insoluble in chloroform, ethanol and ether, but soluble in mixtures of ethanol and methylene chloride.
10. Viscosity: HPMC K4M; HPMCK15M. HPMC K100M;
11. Stability and storage: It is stable although it is slightly hygroscopic. The bulk material should be stored in airtight container in a cold and dry place. Increase in temperature reduces the viscosity of the solution.
12. Safety: It is widely used in many oral and topical pharmaceutical formulations. It is generally regarded as a non-toxic and non-irritant material, although excessive consumption may have laxative effect.
13. Pharmaceutical Applications:
14. Film-former in tablet film coating: Lower viscosity grades are used in aqueous film coating and higher viscosity grades are used in solvent film coating.
15. Binder in tablet granulations: 2.5% high-viscosity grades are used to retard the release of water-soluble drugs.
16. As a Thickening agent: Thickening agent added to vehicles for eye drops & artificial fear solutions at 0.45 - 1.0% concentrations.
17. As a protective colloid: Prevents droplets and particles from Coalescing or agglomerating, thus inhibiting the formation of sediments. It is used as emulsifier, suspending agent & stabilizer in gels & ointments. As an adhesive in plastic bandages.

PREPARATION OF MUCOADHESIVE [85-89] TABLETS

Materials: Metoprolol succinate was gift sample from Mylan laboratories, cabopol-940 from Yarrow Chem. Products, Mumbai.HPMC(K100M,K4M,K15M), Ethylcellulose received from Yarrow Chem. Products, Mumbai. Mcc102, Magnesium stearate and Talc from Molychem, Mumbai.

Mucoadhesive tablets preparation: Metoprolol succinate was mixed manually with different ratios of HPMC, Carbopol-940, MCC (102) as diluent. These are passed through 60≠ sieve except magnesium stearate and talc. All the ingredients were blended in mortor and pestle and this mixture was lubricated with magnesium stearate and talc for 2to3min..Then it was compressed into tablets by direct compression method using 8mm flat faced punches,the ethyl cellulose is given as backing layer. The mass of tablets were determined using Digital balance (Shimdazu, Japan)and thickness of tablets with a digital Screw Gauge.

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In vitro dissolution studies: Dissolution of the tablet of each batch was carried out using USP 2dissolution type II apparatus using paddle, fixing the tablet to the paddle. 900 ml of PH 0.1N Hydrochloric acid dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 370 C ± 0.50 C. The rotation speed of the paddle was set at 50 rpm. 1 ml of sample was withdrawn at predetermined time interval of 1 hr for 12 hrs and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10 ml in 10 ml volumetric flask with distilled water, filtered and analyzed by an UV spectrophotometer at 222 nm using 0.1N HCl as a blank. The drug content was calculated using the equation generated from standard calibration curve. The % cumulative drug release was calculated.

Stability studies of the optimized formulation: Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life.The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established. ICH specifies the length of study and storage conditions.

DATA ANALYSIS

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted in to Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. Based on the r-value, the best-fit model was selected.

Zero order kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area dose not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t$$

Where Q_t = amount of drug dissolved in time t.

Q_o = initial amount of the drug in the solution and

K_o = zero order release constant

First order kinetics: To study the first order release rate kinetics the release rate data were fitted to the following equation,

$$\text{Log}Q_t = \log Q_o + K_1 t/2.303$$

Where Qt is the amount of drug released in time t, Qo is the initial amount of drug in the solution and K1 is the first order release constant.

Higuchi model: Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The equation is, $Q_t = K_H \bullet t_{1/2}$

Where Qt = amount of drug released in time t, KH = Higuchi dissolution constant.

Krosmeyer and Peppas release model: To study this model the release rate data are fitted to the following equation,

$$M_t / M_\infty = K \bullet t^n$$

Where M_t / M_∞ is the fraction of drug release, K is the release constant, t is the release time and n is the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage form.

EX VIVO residence time [90-94]: 900 ml 0.1 N HCl (PH 1.2) maintained at 37±0.5°C was kept in modified USP disintegration apparatus.The mucoadhesive tablet was then attached to a segment of goat stomach mucosa , which was attached to a glass slide fixed vertically to the apparatus, by applying a light force with a finger tip for 30 seconds. Then the tablet and mucosa were hydrated with the medium. The apparatus was allowed to move up and down so that

the tablet was completely immersed in the medium at the lowest point and was out at the highest point. The time for complete erosion or detachment of the tablet from the mucosal surface was recorded as the mucoadhesion time.

Factors effecteing controlling gastric retention of dosage forms: The gastric retention time (GRT) of dosage forms is mainly controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

Oral drug delivery system represents one amongst the most important controllerd drug delivery system , such a dose type having a serious advantage of patient compliance . Gastro long mucoadhesive drug delivery system belongs to oral management drug delivery system , that area unit capable of adhering to abdomen membrane there by bypassing the viscus transit and the release of drug in a controlled manner for a chronic amount of your time the discharge rate are going to be controlled relying upon the sort and concentration of the compound used that swells ,causing diffusion and erosion of the drug.

Metoprolol succinate is a widely used ß1 selective adreno receptor antagonist, is rapidly and completely absorbed from the gastrointestinal track when administration in conventional dosage forms.

The systemic availability after oral administration, however, is only about 50%due to hepatic oxidative metabolism which is subjected to genetic polymorphism. Since Metoprolol has a relatively short elimination half life of 3-7hours having bioavailability (12%).

A simple once daily dosage regimen of a conventional tablet is not sufficient to sustain plasma levels and clinically effective ß1 blockade over the entire day.

For the patient compliance the Metoprolol succinate as sustained release is necessary.

In the present investigation bioadhesive and viscosity enhancing polymers such as Carbopol 940 ,Ethyl cellulose,HPMC K4M , K15M,K100M in different ratios were employed.

Hence, the present research work systematically the effect of formulation variables on the release and bioadhesive properties of Metoprolol succinate.

Nine formulations of mucoadhesive tablets were prepared using various grades of HPMC polymers such as, HPMC K4M, HPMC K15M,HPMCK100M and Carbopol 940 in different ratios the tablet were prepared by direct compression method.

Carbopol and HPMC was used for adhesion strength,here HPMC were employed as viscosity enhancing polymer also. Ethyl cellulose is used as a backing layer to the tablet.

All the formulations were prepared by keeping constant tablet weight of 250mg with an hardness ranging upto5.4- 5.8 kg/cm^2.

The prepared tablets were subjected for preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. Evaluation study indicate that, the values of various parameters were within the pharmacopial permition limits.

Water uptake study (swelling index): Ex vivo studies shown by optimized formula with residence time of 12 hours.

All the nine formulations showed increase in concentration of polymer i.e swelling capacity of tablets also increases. The percentage water uptake of optimised formulation F7 is 126.0.

The in-vitro dissolution studies were carried out in duplicate and the results shown in the tables are mean of replicate values. In vitro release data obtained for formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9. The results obtained for the in vitro drug release for different formulations i.e from F1 to F10 are (F1 TO F3) 94%, 91%, 84%, (F4TOF6) 98%, 93%, 95%, (F7 TO F9) 98%, 91%, 96% and respectively., at the end of 12hours .

The rapid drug dissolution was observed in F1and F3, which release 94% and 91%,84% respectively at the end of 5 hours. The rapid drug dissolution might be due to easy breakdown of particle and rapid absorption of drug into the dissolution medium.

Swelling index was shown to be increased with increase in concentration and viscosity of the polymers, HPMCK4M & HPMC K15M showed less swelling index than HPMC K100M.

In-vitro dissolution studies clearly showed that the formulation containing Carbopol 940 and HPMC K100M, and showed higher drug retardation.

In formulations F7 to F9, an increase in concentration of HPMC K100M was found to retard the drug release (98%, 91%, 96%).

DISCUSSION

Metoprolol succinate is a widely used ß1 selective adreno receptor antagonist, is rapidly and completely absorbed from the gastrointestinal track when administration in conventional dosage forms.
Therefore and attempt made to increase the bioavailability of Metoprolol succinate by retaining the dosage form in stomach for a longer period of time. This is achieved by developing gastroretentive mucoadhesive drug delivery system [95-100].

Mucoadhesive tablet were prepared using various polymers such as Carbopol 940, Hydroxy propylmethyl cellulose K4M, HPMCK100M, HPMCK15M, in different proportions. Other excipients used are Mcc as diluent,Ethylcellulose as backing layer and Magnesium stearate ,Talc as an Lubricating agent. Fourier transform IR confirmed the absence of any drug/ polymer/excipients interaction.
Based on various evaluation parameters formulation F7(polymers used in concentration HPMC -28%,Carbopol 940-4%)was selected as optimized formulation and was further subjected for, Stability study and in vitro retension time,Swelling studies

All the formulation were subjected for Zero order, First order, Higuchi matrix, korsemeyor-peppas model and Hixon-crowell equation and all of them followed zero order release.
All of them followed Non fickian except two formulations.

Stability studies: Stability studies were carried out for optimized formulation F7 as per ICH guidelines at one temperature. The formulation showed good stability and the values were within permissible limit.
The Mucoadhesive drug delivery or gastroretentive drug delivery system can be used as an alternative to conventional dosage forms for the class of drugs which undergoes intestinal or enzymatic degradation.
The release of Metoprolol succinate from mucoadhesive tablet is in a controlled manner.
Infrared spectroscopic studies indicated that the drug is compatible with excipients.
The drug content was uniform in all formulations of prepared tablets.

CONCLUSION

The formulation prepared in combination with Carbopol 940 and HPMCK100M (HPMCK100M-28%and Carbopol940-4%) showed maximum in vitro residence time, in vitro drug release pattern.
Optimized formula followed Zero order,Non fickian and Diffusion controlled release.

Promising control release mucoadhesive Metoprolol succinate tablet have been developed.
From the above experiment data it can be concluded that a successful mucoadhesive control drug delivery system for Metoprolol succinate have been developed by using polymers such as Ethyl cellulose(backing layer), Carbopol940, HPMCK100M.
On the basis of in-vitro release studies and its kinetic data F7 was selected as optimized formulations for designing mucoadhesive tablets of Metoprolol succinate.

Optimized formulation (F7) remained stable for a period of two months when subjected for stability studies.
Thus conclusion can be made that this stable gastroretentive mucoadhesive dosage form of Metoprolol succinate has been developed for controlled release.

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