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Research Article

# MUCOADHESIVE MICROSPHERES OF METOPROLOL SUCCINATE FORMULATION AND IN VITRO EVALUATION STUDIES

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**ABSTRACT**

The design and formulation of mucoadhesive microspheres seem to be a potential candidate as an oral controlled drug delivery system in prolonging the drug retention in GIT, and increasing the bioavailability of drug.**Objective:** The present research has been a satisfactory attempt to formulate a mucoadhesive micro particulate system of controlled release of metoprolol succinate. **Methods:** The investigation has indicated that Emulsification internal gelation technique can be successfully employed to metoprolol Succinate loaded alginate microspheres. The biocompatible polymers like sodium alginate, HPMC K4M, chitosan and PVP K30 can be used to formulate a muco adhesive micro particulate system. **Results:** The scanning electron micrpscopy **(**SEM) analysis of the microspheres revealed that sodium alginate-HPMC K4M and sodium alginate-chitosan microspheres were smooth, spherical and slightly aggregated particles when compared with the microspheres of sodium alginate-PVP K30 which were porous, rough, grossly, discrete spherical. As the polymer concentration was increased the % drug loading decreased and % entrapment efficiency was increased due to increase in the viscosity of the solution. The mucoadhesive microspheres of drug with sodium alginate-chitosan were less adhesive to mucus when compared to sodium alginate-HPMC K4M and sodium alginate- PVP K30 which showed greater adhesive strength. The formulations F1 to F9 were best fitted into first order kinetic model and the drug release from the formulation was by non-fickcian (anomalous) diffusion mechanism. **Conclusion:** The selected formulations F3, F6 and F9 microspheres were stable and compatible at the selected temperature and humidity in storage for 60 days. From the stability studies it was found that there was no significant change in the drug entrapment, release characteristics and *in-vitro* adhesive behavior of the microspheres.

**Key words:** Microsphere, Mucoadhesives, SEM, Drug Entrapment and Stability.

## INTRODUCTION

The previous three decades, the treatment of an intense sickness or an unending ailment has been for the most part achieved by conveyance of medications to patients utilizing different ordinary dose frames like tablets, injectables, as medication transporters. This kind of medication conveyance framework is known to give a provoke arrival of medication. In this manner, to accomplish and additionally to keep up the medication focus inside the remedially successful range required for treatment, usually important to take the regular sort of medication conveyance frameworks a few times each day. This outcomes in a critical change of medication levels in the body [1, 2]. The poor patient consistence; expanded odds of missing the dosage of a medication with short half-life for which visit organization is vital. A normal pinnacle valley plasma focus time profile is acquired which makes accomplishment of steady–state condition troublesome. The unavoidable vacillations in the medication focus may prompt under medicine or overmedication as the Css esteems fall or ascend past the restorative range. The fluctuating medication levels may prompt precipitation of unfavorable impacts like queasiness, heaving, gastric disturbance and poisonous quality particularly of a medication with little remedial list at whatever point overmedication happens. Ceaseless I.V. mixture has been perceived as a prevalent method of foundational medicate conveyance that can be custom-made to keep up a consistent and supported medication levels inside restorative window for whatever length of time that required for powerful treatment. It likewise gives a methods for direct passage into the fundamental course of medications that are subjected to hepatic first-pass effect or potentially associated with delivering gastrointestinal contradiction. Sadly, such a method of medication organization involves certain wellbeing risks and in this manner requires persistent hospitalization amid treatment and requires close medicinal supervision [1-9]. As of late streamlining method were utilized definition improvement for individual and consolidate impacts of components employed10-20.To copy the advantages of intravenous medication imbuement without its potential risks, a few specialized progressions have been made. There are two different ways to defeat the circumstance: Development of new, better and more secure medications with long half-lives and vast helpful records. Powerful and more secure utilization of existing medications through ideas and strategies of controlled medication conveyance systems [21-31].

Metoprolol Succinate is a β1 adreno-receptor opponent by and large utilized in angina pectoris, hypertension and Ischemic heart maladies. It has an oral bioavailability of half due to its poor retention in lower gastro intestinal tract. It experiences hepatic digestion and its half-life is around 3-7 hrs. Metoprolol Succinate is accounted for to be less caught up in the lower some portion of the digestive system. Because of the short half-existence of Metoprolol Succinate, various dosages should be taken keeping in mind the end goal to keep up a steady plasma fixation for a decent remedial reaction. The upkeep of a consistent plasma level of a cardiovascular medication is vital in guaranteeing the coveted remedial reaction. Subsequently, metoprolol Succinate is reasonable possibility for the planning of mucoadhesive microspheres in accomplishing a decent helpful reaction. Keeping the above actuality in view the present work is gone for getting ready diverse mucoadhesive details of metoprolol Succinate utilizing distinctive polymers. The sythesis of these plans was chosen by utilizing enhancement procedure. Impact of different components like medication to polymer proportion, polymer to polymer proportion and polymer review on the reaction parameters like span of mucoadhesion, t1/2 and discharge rate co-productive was contemplated. Discharge rate example of medication from the planned details was resolved and from the acquired information instrument of medication discharge was proposed to finish up the system of medication discharge rate

energy. To perform compatibility on medication and polymers and to build up their similarity in detailing utilizing FTIR.To plan mucoadhesive microspheres of Metoprolol Succinate utilizing sodium alginate, HPMC K 4M, chitosan and poly vinyl pyrrolidone (PVP K30) in blends by emulsification - inner gelation system. Physical portrayal of microspheres which incorporates Particle measure examination, Determination of molecule shape and surface morphology, Percentage yield, Drug stacking, Drug capture proficiency, In-vitro mucoadhesion test32, In-vitro tranquilize discharge ponders, In-vitro sedate discharge energy. To do the quickened solidness thinks about on chosen plans.

**MATERIALS AND METHODS**

Metoprolol Succinate was procured from Yarrow Chem products, Mumbai.Glacial acetic acid was purchased from Finar Chemicals Limited., Ahmedabad.Chloroform, Span 80, calcium chloride, sodium alginate and chitosan are procured from S D Fine ChemLimited, Mumbai.HPMC K4M was procured from Noveon Chemicals, Mumbai.

**METHODS**

IR Spectroscopy

The FTIR spectrum of the obtained sample of drug was compared with the standard FTIR spectra of the pure drug.

FTIR range of medication and physical blend of medication with polymers were gotten on FTIR instrument. The examples were blended with KBr. The range was looked over the wave number scope of 4000-400 cm-1. IR affirms the character of the medication and to identify the cooperation of the medication with the transporters.

Preparation of Metoprolol Succinate Mucoadhesive microspheres by Emulsification internal gelation technique

Microspheres containing metoprolol succinate were readied utilizing sodium alginate in mix with HPMC K4M, chitosan and PVP K30 formulae appeared in Table 1. The homogeneous polymer(s)and cross-connecting operator were added to the polymer arrangement and blended altogether by mixing attractively to frame a thick scattering which was then expelled through a syringe with a needle of size no. 23 into light fluid paraffin containing 1.5% range 80 and 0.2% frosty acidic corrosive being held under attractive mixing at 100 rpm. The microspheres were held in the light fluid paraffin for 30 min to deliver inflexible discrete particles. They were gathered by decantation and the item in this manner isolated was washed with chloroform to expel the hints of paraffin oil.

**ASSESSMENT OF MUCOADHESIVE MICROSPHERES**

**Percentage Yield**

The arranged microspheres of all clumps were precisely gauged. The deliberate weight of arranged microspheres was partitioned by the aggregate sum of all the excipients and medication utilized in the planning of the microspheres, which give the aggregate rate yield of mucoadhesive microspheres. It was computed by utilizing following condition.

**% Yield = real weight of item/add up to weight of excipients and medication × 100**

**Particle Size Determination**

The molecule size of the microspheres was controlled by utilizing optical microscopy technique. Around 100 microspheres were meant molecule measure utilizing an aligned optical magnifying instrument.

**Morphological Study utilizing SEM**

The morphological investigation was completed by Scanning Electron Microscope (SEM). Microspheres were checked and inspected under Electron Microscope HITACHI SU 1500, Japan associated with Fine coat, JEOL JFC-1100E Ion sputter. The example was stacked on copper test holder and sputter covered with carbon pursued by Gold.

**Drug Entrapment**

Microspheres proportionate to 50 mg of the medication were taken for assessment. The measure of medication captured was evaluated by pounding the microspheres and separating with aliquots of pH 7.4 phosphate supports over and again. The concentrate was exchanged to a 100 ml volumetric jar and the volume was made up utilizing pH 7.4 phosphate cradle. The arrangement was sifted and the absorbance was estimated after reasonable weakening spectrophotometrically (UV 1700, Shimadzu, Japan) at 224 nm against suitable clear.

**In-vitro wash-off test for Mucoadhesion**

The mucoadhesive property of the microspheres was assessed by an in-vitro grip testing strategy known as the wash-off technique. A 1 cm2 bit of rodent intestinal mucosa was tied onto a glass slide (3-inch by 1-inch) utilizing string. Around 100 microspheres were spread onto the wet, washed, tissue example and the readied slide was clung to the arm of a USP tablet deteriorating test machine. At the point when the crumbling test machine was worked, the tissue example was given a moderate, general up-and-down development in the test liquid (400 ml) at 37±0.5ºC contained in a 1000 ml vessel of the machine. Toward the finish of 1 h, and at hourly interims up to 10 h, the machine was halted and the quantity of microspheres as yet holding fast to the tissue was checked. The test was performed in recreated intestinal liquid (pH 7.4 phosphate cradle).

***In-vitro* Release Study**

The medication discharge think about was performed for microspheres containing amount comparable to 100 mg of Metoprolol Succinate by utilizing USP disintegration contraption Type I in 900 ml of disintegration media at 100 rpm and 37±0.5°C temperature. Distinctive disintegration medium (pH 1.2 hydrochloricacid and pH 7.4 phosphate cradled arrangement) was utilized for metoprolol succinate discharge test. 5 ml of test was pulled back at foreordained time interim for12 h and same volume of new medium was supplanted to kept up sink condition. The pulled back examples were separated through a 0.45 µm layer channel, weakened reasonably and measured spectrophotometrically at 224 nm. The combined % sedate discharge was ascertained utilizing standard adjustment bend.

**Release Kinetics**

The framework frameworks were accounted for to pursue the Peppas discharge rate and the dispersion instrument for the arrival of the medication. To examine the instrument for the discharge and discharge rate energy of the dose frame, the information acquired was fitted in to, Zero request, First request, Higuchi network, Peppas and Hixson Crowell show. In this by looking at the r-values acquired, the best-fit model was chosen.

**Zero Order Kinetics**

Medication dissolution from Pharmaceutical measurements shapes that don't disaggregate and releasethe tranquilize gradually, expecting that the territory does not change and no balance conditions are obtained can be spoken to by the accompanying condition:

Qt = Qo + Kot

Where,

Qt = Amount of medication broke up in time t
Qo = Initial measure of medication in the arrangement and
Ko = Zero request discharge steady

First Order Kinetics

To consider the primary request discharge energy the discharge rate information were fitted to the followingequation. Log Qt = log Qo + K1t/2.303 Where, Qt = Amount of medication discharged in

time t, Qo = Initial measure of medication in the arrangement and K1 = First request discharge consistent.

**Higuchi Model**

Higuchi built up a few hypothetical models to contemplate the arrival of water solvent and low soluble drugs incorporated in semi-solidand/or solid matrixes. Scientific articulations were acquired for medication particles scattered in a uniform grid acting as the dispersion media. The Higuchi condition is

Qt = KH × t1/2

Where, Qt = measure of medication discharged in time t and KH = Higuchi disintegration consistent

Korsmeyer-Peppas Model: To ponder this model, the discharge rate information is fitted to the accompanying condition. Mt/M = K. tnWhere, Mt/M = Fraction of medication release,K = Release constantt = Drug discharge time andn = Diffusional type for the medication discharge that is reliant on the state of the network measurements frame. The estimations of 'n' will be, n = 0.45 Fickian (case I) discharge, 0.45 < n < 0.89 Non-Fickian (Anomalous) discharge, n = 0.89 Case II (Zero request) discharge, > 0.89 Super case II compose discharge.

**Hixson– Crowell Model**

To examine the Hixson– Crowell display, the discharge rate information are fitted to the accompanying condition. Wo1/3–Wt1/3/Ks t Where, Wo = Amount of medication in the pharmaceutical measurement shape, Wt = Remaining measure of medication in the pharmaceutical dose frame Ks = Constant consolidating the surface-volume connection

**Stability Studies**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions. ICH guidelines the length of study and storage conditions: Accelerated testing - 40°C/75% RH for 6 months. The accelerated stability study of the best formulations was carried out as per the ICH guidelines.

**RESULTS AND DISCUSSION**

FTIR spectrum of the Metoprolol Succinate pure drug was found to be similar to the standard spectrum of metoprolol Succinate as in I.P. The spectrum of metoprolol Succinate (pure drug) and spectrum of metoprolol succinate with polymer sodium alginate along with copolymers HPMC K4M, chitosan and PVP K30 showed the following functional groups at their frequencies. From the FT-IR spectra of the pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristic peaks of Metoprolol Succinate were present in the combination spectra as well thus indicating the compatibility of the drug with the polymers used. The individual FT-IR spectra of the pure drug metoprolol Succinate, as well as the combination spectra of the drug and polymers are shown in the Figure 1 and Table 2.

**Percentage yield**

Percentage yield of different formulation F1 to F9 were calculated and the yield was found to be 79.1%, 75.4%, 67.8%, 81.2%, 77%, 70.2% 83.7%, 76.52% and 69.3% respectively. The percentage practical yield slightly decreased as the polymer ratio increased.

**Particle Size Analysis**

Average particle size of microspheres as determined by optical microscopy by using stage micrometer and ocular micrometer are shown in Table.3. The mean particle size for the formulation F7 to F9 containing sodium alginate-PVP K30 was found to be in range from 851±8.69 µm to 913±12.51 µm. For formulation F4 to F6 containing sodium alginate-chitosan, the mean particle size was found to be in range from 807±7.14 µm to 908±12.24 µm and for formulation F1 to F3 containing sodium alginate-HPMC K4M was found to be in range from 884±6.35 µm to 1007±12.42 µm respectively. With increase in polymers concentration in the microspheres from F1 to F9, the particle size of microspheres increases respectively. This is because the viscosity of the polymer solution increases with increasing polymer concentration, which in turn decreases the stirring efficiency.

**Scanning Electron Microscopy**

The determination of shape and surface morphology was done by scanning electron microscope HITACHI SU 1500, Japan. SEM analysis of the samples revealed that all microspheres prepared were spherical in shape.The microspheres of Metoprolol Succinate with sodium alginate-HPMC K4M, sodium alginate-chitosan were smooth, spherical and slightly aggregated particles when compared with the microspheres of Metoprolol Succinate with sodium alginate-PVP K30 which were porous, rough, grossly, discrete spherical. Scanning electron photomicrographs of the formulations F3, F6 and F9 are shown in Fig.3, Fig.4 and Fig.5.

**Table 1: Formulation of Metoprolol Succinate Mucoadhesive Microspheres**

| Formulation | Metoprolol succinate (mg) | Sodium Alginate (mg) | HPMC K4M (mg) | Chitosan (mg) | PVP K30 (mg) |
|---|---|---|---|---|---|
| F1 | 100 | 50 | 50 | - | - |
| F2 | 100 | 50 | 100 | - | - |
| F3 | 100 | 50 | 150 | - | - |
| F4 | 100 | 50 | - | 50 | - |
| F5 | 100 | 50 | - | 100 | - |
| F6 | 100 | 50 | - | 150 | - |
| F7 | 100 | 50 | - | - | 50 |
| F8 | 100 | 50 | - | - | 100 |
| F9 | 100 | 50 | - | - | 150 |

**Fig. 1: FTIR Spectra of Metoprolol Succinate with Sodium alginate, HPMC K4M, Chitosan and PVP K30**

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**Table 2: Average Particle Size of Metoprolol Succinate Mucoadhesive Microspheres**

| Formulation | Average particle size (µm)±SD |
|---|---|
| F1 | 884±6.35 |
| F2 | 940±11.28 |
| F3 | 1007±12.42 |
| F4 | 807±7.14 |
| F5 | 876±10.73 |
| F6 | 908±12.24 |
| F7 | 851±8.69 |
| F8 | 883±11.46 |
| F9 | 913±12.51 |

**Table 3: In Vitro Drug Released Profile**

| Time(hr) | Cumulative Percent Drug Release(n=3) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **1** | 13.76 | 13.1 | 12.6 | 16.2 | 14.7 | 13.7 | 14.1 | 14.4 | 13.5 |
| **2** | 22.94 | 20.3 | 18.5 | 30.6 | 28.5 | 24.7 | 27.2 | 24.6 | 24.5 |
| **3** | 36.29 | 31.4 | 27.4 | 42.7 | 40.4 | 38.8 | 40.3 | 38.5 | 36.7 |
| **4** | 42.74 | 40.2 | 38.4 | 54.3 | 51.3 | 50.9 | 50.3 | 47.4 | 46.5 |
| **5** | 53.49 | 51.4 | 47.2 | 64.2 | 59.5 | 57.5 | 58.4 | 62.1 | 54.4 |
| **6** | 57.5 | 55.3 | 51.3 | 71.1 | 66.6 | 64.4 | 65.5 | 68.4 | 61.5 |
| **7** | 62 | 60.2 | 53.2 | 75.3 | 71.6 | 68.5 | 73.3 | 72.4 | 65.8 |
| **8** | 70 | 68.2 | 57.1 | 79.4 | 76.4 | 70.6 | 74.4 | 73.6 | 68.9 |
| **9** | 75 | 72.3 | 62.5 | 83.1 | 80.5 | 74.7 | 77.5 | 74.7 | 71.8 |
| **10** | 77 | 74.1 | 65.6 | 85.2 | 81.8 | 75.8 | 80.6 | 77.4 | 73.5 |
| **11** | 80 | 77.3 | 68.4 | 86.3 | 83.7 | 77.6 | 82.4 | 79.8 | 74.4 |
| **12** | 82 | 79.5 | 72.3 | 88.4 | 84.5 | 78.6 | 84.3 | 81.4 | 75.4 |

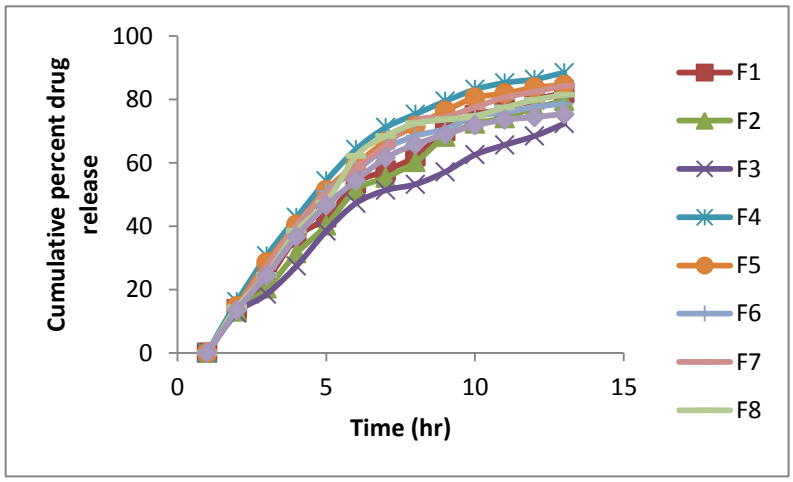


**Fig.2: In vitro drug released profile.**

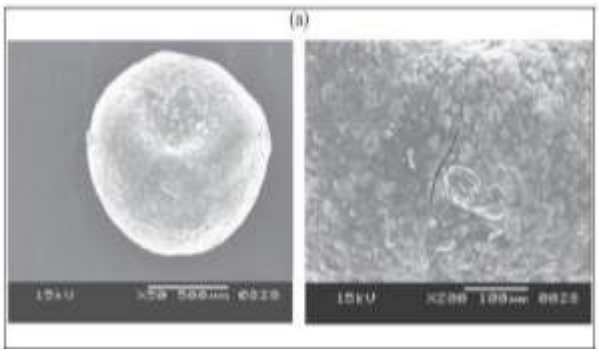


**Fig.3: SEM F3 Formulation.**

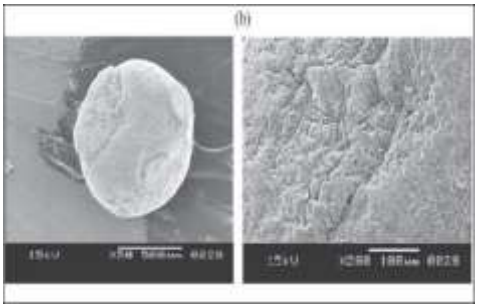

**Fig.4: SEM of F6 formulation**

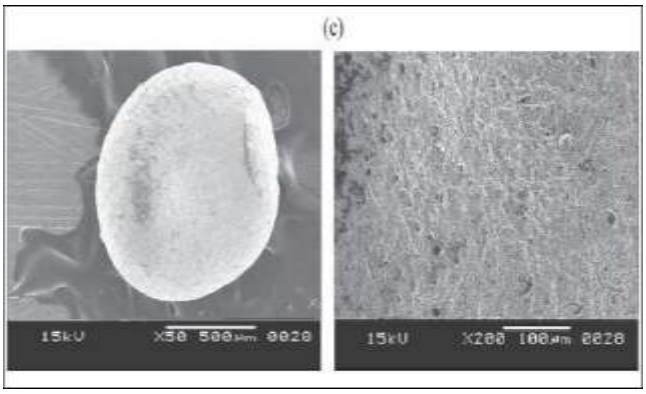


**Fig.5: SEM of F9 Formulation**

**Table 4: Drug Loading and Drug Entrapment of Metoprolol Succinate Mucoadhesive Microspheres**

| Formulation Code | Actual Drug Content (mg) | Theoretical Drug Content (mg) | Total Weight of Microspheres (mg) | % Drug Loading | %Drug Entrapment |
|---|---|---|---|---|---|
| F1 | 20.47 | 25 | 50 | 35.42 | 81.88 |
| F2 | 16.59 | 20 | 50 | 33.18 | 82.94 |
| F3 | 15.58 | 16.67 | 50 | 29.24 | 93.48 |
| F4 | 16.79 | 25 | 50 | 33.58 | 67.16 |
| F5 | 15.26 | 20 | 50 | 30.52 | 76.31 |
| F6 | 13.97 | 16.67 | 50 | 27.94 | 83.79 |
| F7 | 17.71 | 25 | 50 | 40.94 | 70.86 |
| F8 | 15.67 | 20 | 50 | 31.34 | 78.35 |

**Table.5 Stability studies for Formulations stored 40°C/75% RH**

| Time in Days | Percent Drug Entrapment | | | Percent Mucoadhesion | | | Percent Cumulative Drug Release | | |
|---|---|---|---|---|---|---|---|---|---|
| | F3 | F6 | F9 | F3 | F6 | F9 | F3 | F6 | F9 |
| **15** | 93.46 | 83.7 | 87.70 | 95.57 | 81.10 | 84.3 | 72.65 | 84.29 | 75.85 |
| **30** | 93.41 | 83.66 | 87.67 | 95.55 | 81.07 | 84.26 | 72.63 | 84.27 | 75.75 |
| **45** | 93.37 | 83.65 | 87.60 | 95.54 | 81.05 | 84.22 | 72.63 | 84.26 | 75.64 |
| **60** | 93.32 | 83.65 | 87.54 | 95.50 | 81.04 | 84.19 | 72.60 | 84.23 | 75.60 |

**Drug Loading and Drug Entrapment**

As the polymer concentration was increased the % drug loading decreased and % entrapment efficiency was increased due to increase in the viscosity of the solution. This can be attributed to the permeation characteristics of each polymer used, that could facilitate the diffusion of part of entrapped drug to the surrounding medium during preparation of mucoadhesive microspheres. Microspheres with sodium alginate-HPMC K4M showed higher incorporation efficiency than those with sodium alginate-PVP K30 and sodium alginate chitosan shown in table 4.

The results obtained from in-vitro drug release were plotted adopting five different mathematical models of data treatment as follows zero order rate kinetics, first order rate kinetics, Higuchi model, Peppas exponential equation and Hixson % Cumulative Drug Release Vs. Time (Zero order rate kinetics), Log % Cumulative Drug Retained Vs. Time (First order rate kinetics), Percent Cumulative Drug release was plotted against √T (root time). (Higuchi model), Log % Cum. Drug Release Vs. Log Time (Peppas exponential equation) Hixson-Crowell's erosion equation, (% Cum. Drug Retained)1/3 Vs. Time. The curve fitting results of the release rate profiles of the designed formulations are shown in the Table 3 and Figure 2. Which gave an idea on the release rate and the mechanism of release. The values were compared with each other for model and drug equation as shown based on the highest regression values (R2), fitting of the release rate data to various models revealed that all the formulations (F1 to F9) follow first order release kinetics with regression values ranging from 0.9552 to 0.9960. All the formulations were subjected to Korsmeyer-Peppas plots, 'n' value ranges from 0.4196 to 0.4992 indicating that

the drug release was by non-fickian (anomalous) diffusion mechanism. Stability study was conducted for the prepared mucoadhesive microspheres of formulation F3, F6 and F9 at 40°C/75% RH respectively for a period of 60 days. Then, the samples were analyzed for drug release studies of the microsphere at the end of 15, 30, 45 and 60 days. The results of stability studies are given in the Table.5.There was no significant change in the entrapment efficiency, mucoadhesion and In vitro release study of the microspheres.

**CONCLUSION**

The present study has been a satisfactory attempt to formulate a mucoadhesive micro particulate system of metoprolol succinate with a view of improving its oral bioavailability and giving a controlled release of the drug. From the study following conclusions could be drawn. The results of this investigation have indicated that Emulsification internal gelation technique can be successfully employed to fabricate metoprolol Succinate loaded alginate microspheres. FTIR study shows no significant shifting of the peaks therefore it confirms the short term stability of the drug in the microspheres. Biocompatible polymers like sodium alginate, HPMC K4M, chitosan and PVP K30 can be used to formulate a muco adhesive micro particulate system.Micromeritic studies revealed that the mean particle size of the prepared microspheres was within the range of 807±7.14 to 1007±12.42 µm, to 908±12.24 µm and are suitable for bioadhesive microspheres for oral administration.SEM analysis of the microspheres revealed that sodium alginate-HPMC K4M and sodium alginate-chitosan microspheres were smooth, spherical and slightly aggregated particles when compared with the microspheres of sodium alginate-PVP K30 which were porous, rough, grossly, discrete spherical. Good percentage of drug entrapment and practical yields were obtained with all the polymers. As the polymer concentration was increased the % drug loading decreased and % entrapment efficiency was increased due to increase in the viscosity of the solution. The mucoadhesive microspheres of drug with sodium alginate-chitosan were less adhesive to mucus when compared to sodium alginate-HPMC K4M and sodium alginate- PVP K30 which showed greater adhesive strength.Cumulative percentage drug release significantly decreased with increase in polymer and copolymer concentration. The overall curve fitting into various mathematical models was found to be on an average. The formulations F1 to F9 were best fitted into first order kinetic model and the drug release from the formulation was by non-fickcian (anomalous) diffusion mechanism.Selected F3, F6 and F9 formulated microspheres were stable and compatible at the selected temperature and humidity in storage for 60 days.From the stability studies it was found that there was no significant change in the drug entrapment, release characteristics and in-vitro adhesive behavior of the microspheres. Thus, the formulated mucoadhesive microspheres seem to be a potential candidate as an oral controlled drug delivery system in prolonging the drug retention in GIT, and increasing the bioavailability of drug.

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