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Original Article

Formulation development and in-vitro evaluation of dexlansoprazole loaded double walled microspheres

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ABSTRACT

In the present work, double walled microspheres of Dexlansoprazole using Sodium alginate, HPMC E15, Xanthan gum, Ethyl cellulose as copolymers and along with Carbopol were formulated to deliver Dexlansoprazole through oral route. Details regarding the preparation and evaluation of the formulations have been discussed in results. From the study following conclusions could be drawn. The results of this investigation indicate that Ion gelation method can be successfully employed to fabricate Dexlansoprazole microspheres. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used. Microspheres containing sodium alginate along with carbopol and HPMC E15 in 1:1.5 ratios had a least size range of 12µm.Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, and Particle size. The *invitro* drug release decreased with increase in the polymer and copolymer concentration. Among all formulations DL6 shows Maximum drug release in 12^{th} hr when compared with other formulations. Analysis of drug release mechanism showed that the drug release from the formulations followed the Non fickian diffusion mechanism and follows zero order kinetics. Based on the results of evaluation tests formulation coded DL6 was concluded as best formulation.

Key words: Carbopol , Microspheres , Diffusion , Kinetics , Co-polymers.

INTRODUCTION

Controlled Drug Delivery System: For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosol , injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often

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necessary to take this type of drug delivery systems several times a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems. Controlled release systems include any drug delivery system that "achieves slow release of the drug over an extended period of time." If the system can provide some control weather this is of a temporal or spatial nature, in other words, if the system is successful in maintaining predictable and reproducible kinetics in the target tissue or cell, it is considered as a controlled release system.

Microencapsulation: Microenacapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded or enclosed, by an intact shell. Two major classes of microencapsulation methods have evolved i.e. chemical and physical. It provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection, and of controlling the release characteristics or availability of coated materials. The first class of encapsulation method involves polymerization during the process of preparing the microcapsules. The second type involves the controlled precipitation of a polymeric solution where in physical changes usually occur.

Double Walled Microspheres

Present microsphere delivery system technology consisting of a single drug dispersed within a polymer matrix has several drawbacks. One is the problem of the so-called "burst effect". By exploiting the phenomenon of phase separation between two immiscible polymers dissolved in a mutual solvent, a double-walled microsphere could be manufactured with the second polymer coating the polymer/drug matrix.

This one-step process would give a consistent coating of even very small microspheres not achievable via normal, two-step coating processes and would help to smooth out the release curve by lessening the "burst effect". Along with solving the problem of the "burst effect", this concept of double-walled microspheres could be used to achieve constant release of the drug over long periods of time. So far, this has only been achieved with a limited number of geometric configurations. Since every polymer has its own characteristic release rate, the release could be kept much more constant by changing the polymer type and/or properties. By combining these layers so that the release rate of one layer would complement the slowing of release due to decreased surface area or increased diffusion distances.

Advantages

- Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
- Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles *in vivo.*
- Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.

Limitation

some of the disadvantages were found to be as follows:

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.

MATERIALS AND METHODS

Dexlansoprazole was procured from Chandra labs Hyderabad. Xanthun gum, Carbopol, HPMC E15, Ethyl cellulose, Sodium alginate was supplied from standard chemicals, & Avantor chemicals. All other chemicals and reagent used were of analytical grade.

Estimation of Dexlansoprazole:

Standard Graph of Dexlansoprazole:

Standard Stock solution: 10 mg of Dexlansoprazole was soluble in less amount of Methanol & made up to 10 ml with 0.1N Hydrochloric acid to get 1000 µg/ml.

Scanning: From the stock solution 100µg/ml was arranged & allow to UV scan in b/w 200- 400 nm. The max absorbance was originated to be 281nm.

Linearity of Dexlansoprazole in 0.1 N HCL & 6.8 pH buffer: The additive concentration has prepared by correct dilutions from the 1st stock & dilutes various conc. such as 0.2ml-1ml with the

buffer to get 2-10µg/ml of pure sample of Dexlansoprazole. The concentration of Dexlansoprazole lives in the microspheres was attaining from the Linearity.

Drug-Excipients Compatibility study: Prior to the development of the dosage forms the preformulation study was carried out. IR spectral studies lies more in the qualitative identification of substances either in pure form or in combination with polymers and excipients and acts as a tool in establishment of chemical interaction. FTIR spectra were recorded with a Thermo Nicolet. Japan In the range 400–4000 cm−1 using a resolution of 4 cm−1 and 16 scans. Samples were diluted with KBr mixing Powder, and pressed to obtain self-supporting disks. Liquid samples formulations were analyzed to form a thin liquid film between two KBr disks.

Preparation of Double Walled Microspheres of Dexlansoprazole: The double walled microspheres were prepared by two step process. In first step the core microspheres of sodium Alginate and with different polymers were formulated. The microspheres then dispersed in the organic phase. The organic phase containing polymer in which drug was dissolved then the organic phase was emulsified with liquid paraffin. The solvent was allowed to evaporate and double walled microspheres were collected.

Formulation of Core Microspheres with Drug:

- Dexlansoprazole and all other polymers were individually passed through sieve no#60.
- The required quantities of Sodium alginate and the polymer were dissolved in purified water to form a homogenous polymer solution.
- The Drug, Dexlansoprazole was added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion.
- The resulting dispersion was then added manually drop wise into calcium chloride (1.5 % w/v) solution through a syringe with a needle of size no. 22.
- The added droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce the spherical rigid microspheres.
- The microspheres were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45^0C for12 hours.

Formulation of Double Walled Microspheres: The previously formulated microspheres were dispersed in the organic phase. The second polymer 3%HPMC Phthalate was dissolved in the same organic phase. The resulting organic phase solution was emulsified in liquid paraffin. 1% span 80 solutions were used as emulsifying agent. Above emulsion was stirred for complete evaporation of the organic solution. After complete evaporation of the organic solution the double walled microspheres were collected by vacuum filtration and washed with n-hexane. The resulted double walled microspheres were freeze dried for 24hrs. formulation table was represented in table no.1.

Evaluation of Microspheres:

Drug Entrapment Efficiency: Microspheres of DL1 to DL7 Formulations in each formulation equivalent to 60mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of pH6.8 Phosphate buffer repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using pH6.8 Phosphate buffer. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 281 nm against appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas:

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Determination of Percentage Yield: The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula:

$$\textbf{Percentage yield} = \frac{\textbf{Practical yield (mg)}}{\textbf{Theoretical yield}} \times 100$$

In-vitro Release Study: The drug release study was performed for DL1 to DL7 formulations microsphere containing quantity equivalent to 60mg of Dexlansoprazole Microspheres by using USP dissolution apparatus Type I in 900 ml of 0.1 N HCL for first 2hrs then replaced with pH6.8 Phosphate buffer dissolution media at 100 rpm and 37^0C temperature. 10 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 281 nm. The cumulative % drug release was calculated using standard calibration curve.

Release Kinetics: The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi

matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected.

RESULTS AND DISCUSSION

Scanning of Dexlansoprazole: In order to determine the maximum wavelength (λ_{max}) of Dexlansoprazole, 10 µg/mL of solutions in 0. 1 N HCl was prepared and scanned using UV spectrophotometer within the wavelength range of 200 - 400 nm against 0.1 N HCl as blank. The absorption curve showed characteristic absorption maximum at 281 nm for Dexlansoprazole.

Linearity of Dexlansoprazole in 0.1 N HCL & 6.8 pH buffer: Calibration curve of Dexlansoprazole was constructed in 0.1 N HCl & 6.8 pH buffer at maximum wavelength of 281 nm and analysed for regression analysis. Regression analysis was selected because it minimize the deviation and correct the variance heterogeneity. The regression line was defined by its slope (m=0.074), intercept (C=0.016) & slope (m=0.073), intercept (C=0.003) for normal regression analysis was found as 0.1N HCl and 6.8pH buffer, respectively, with regression coefficient of 0.998 respectively.

Percentage yield (%):

The results of percentage yield of prepared Dexlansoprazole loaded double walled microspheres were found in the range of 76.2% to 87.9%. The results was tabulated in table no 2.

Percentage Drug Entrapment Efficiency: The results of Dexlansoprazole double walled microspheres % drug entrapment efficiency was found within 72.7% to 88.6%. The results were tabulated in table no 2.

Invitro drug release studies: As per the results of dissolution data of preparations having Xanthan gum, Carbopol, HPMC E15 **DL5 – DL7** carried out for 12 hrs, the max drug discharge is observed for formulation DL6 at 12th hr (98.64%). Hence the final preparation consider as DL6. Results were figured out in fig no.3.

CONCLUSION

In the present study, double walled microspheres of Dexlansoprazole were prepared using Na alginate, HPMC E15, Xanthan gum, EC as copolymers along with Carbopol 934. The obtained result through the conducted analysis by ionotropic gelation technique can be sucessfully employed to the frabricate Dexlansoprazole microspheres. IR for the obtained blend shows that the Dexlansoprazole is well suitable with the used excipients. Microspheres having Na alginate along with HPMC E15 and carbopol in 1.5:1 proportion have dimension array of approximately 12µm. By increase in polymers concentration there is increase in %yield, % drug entrapment efficiency, Particle size. The invitro drug release decreased by addition of the polymer and co polymer concentration. The design of DL6 s sodium alginate with HPMC E15 showed as maximum release of 98.64 % at 12 hours. The drug release of formulation is best fit for higuchi's model & drug release follows zero order kinetics. Based on above results the evaluation studies formulation VR4 is concluded as best formulation.

Table 1: Formulations of Microspheres

Ingredients (%)	DL1	DL2	DL3	DL4	DL5	DL6	DL7
Dexlansoprazole (mg)	60	60	60	60	60	60	60
HPMC E 15	1.5	-	-	2	2	2	2
Ethyl cellulose	-	1.5	-	-	-	-	-
Xanthun gum	-	-	1.5	-	-	-	-
Carbopol	0.5	0.5	0.5	0.5	0.5	1	1
Sodium alginate	1	1	1	1	1.5	1.5	1

Table 2: The designed microspheres of % yield & % drug entrapment efficiency

Formulation code	% yield	% Drug entrapment efficiency
DL1	76.2	72.7
DL2	79.5	74.6
DL3	82.7	82.8
DL4	87.9	86.7
DL5	78.6	88.1
DL6	86.7	87.9
DL7	82.9	88.6

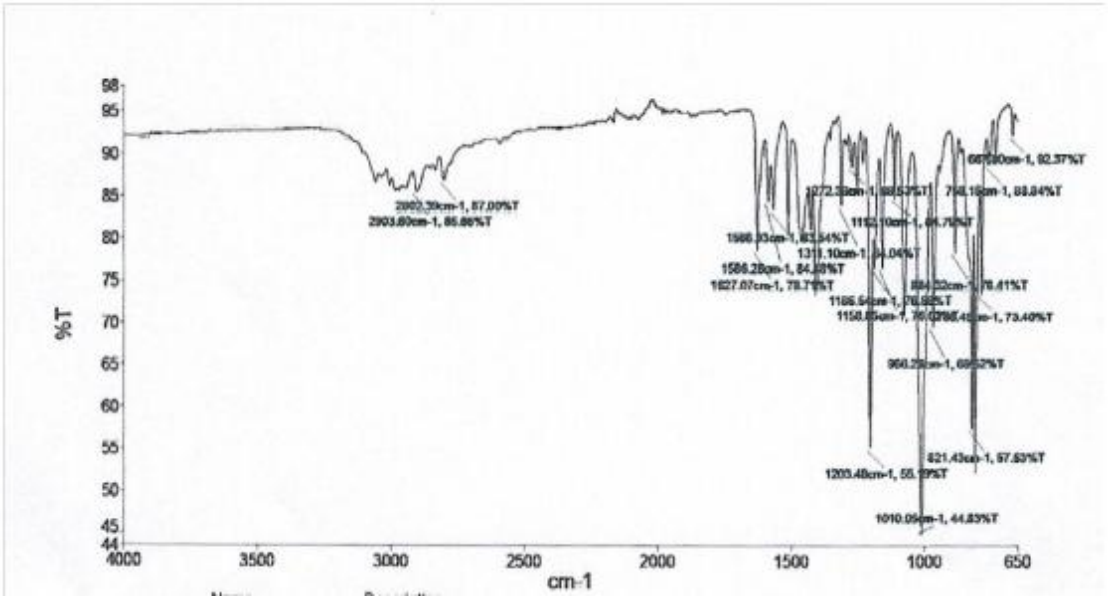

Fig No 1: FTIR Spectra of Dexlansoprazole pure drug

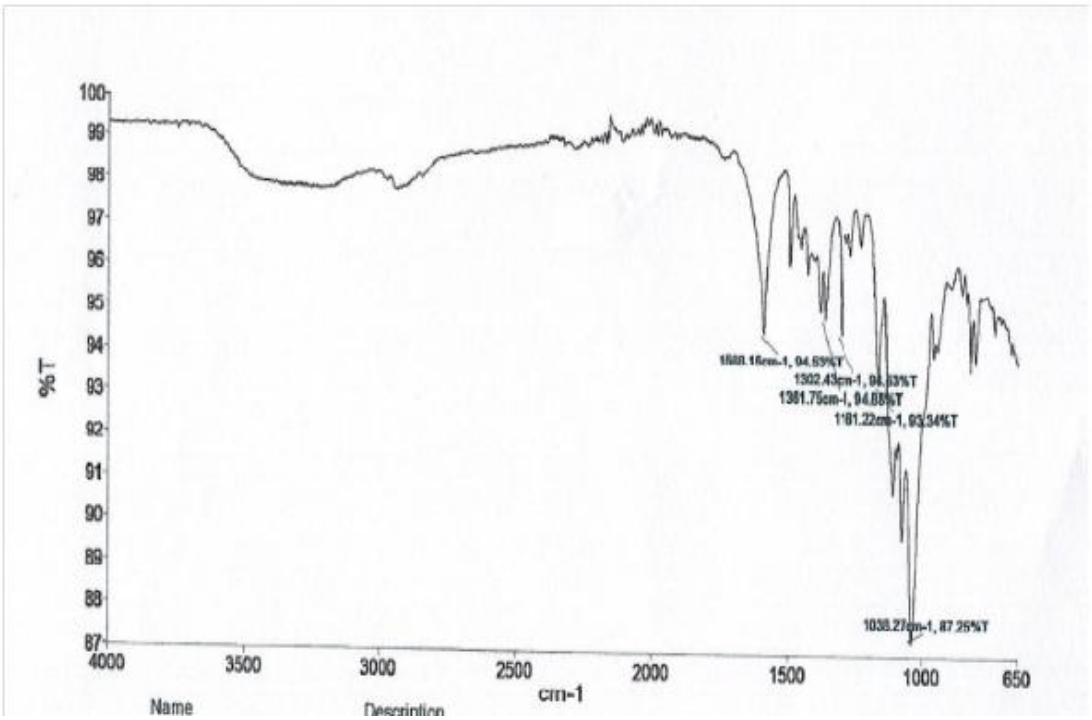

Fig No 2: FTIR Spectra of Dexlansoprazole final Formulation

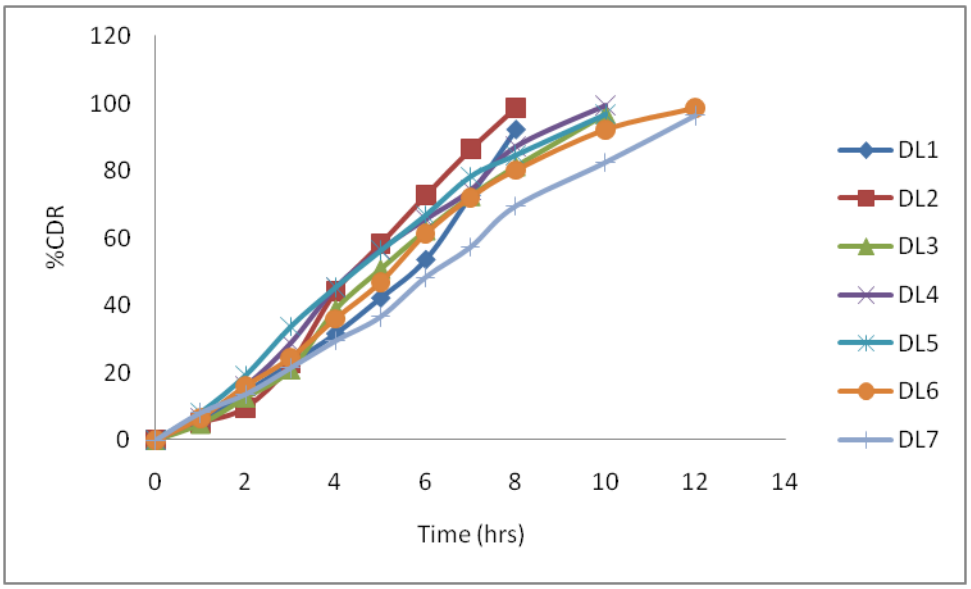

Fig 3: In-Vitro drug discharge of Dexlansoprazole microspheres DL1 – DL4 formulations

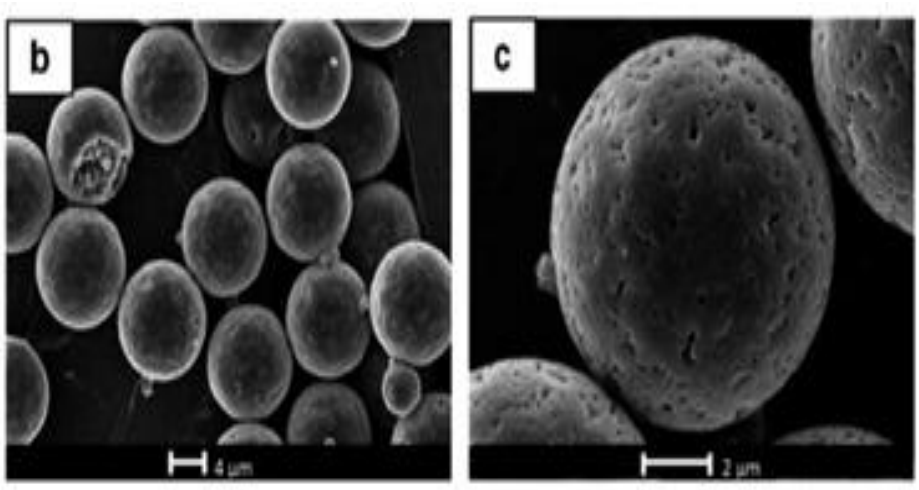

Fig 4: SEM of Double walled microspheres of Dexlansoprazole

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