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Development and Characterization of Repaglinide loaded blend Microsphere

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Abstract

The current study aimed to develop controlled-release tablets of Repaglinide utilizing blend microspheres comprising two or more polymers. Repaglinide, a widely used anti-diabetic drug, is known for its relatively short plasma half-life of approximately 3-4 hours, necessitating frequent dosing to maintain therapeutic blood levels for long-term diabetes treatment. To address this limitation, various strategies have been explored to enhance Repaglinide's bioavailability and extend its drug release profile, thus reducing the need for frequent dosing. One such approach is the use of blend microspheres in the formulation of controlled-release tablets.

Key words: Blend Microsphere, Repaglinide, Enhance Bioavailability, poly lactic acid, poly caprolactone

Introduction

To achieve optimum therapeutic effectiveness, the agent must be delivered to the target tissue in the appropriate quantity and at the right moment, resulting in reduced poisonousness and reaction. There are some methods for supplying a medicinal drug to the specific position in a managed and persistent way. Using microspheres as drug carriers is one such process. A microsphere is a "monolithic sphere or therapeutic agent spread in the matrix and as a molecular dispersion of particles" (or) drug particles are dispersed at the molecular level in a system which made from the continuous phase of one or more than one miscible polymers . Microspheres are free-flowing, tiny and spherical units composed of proteins or synthetic polymers with diameters in the micro metre scale (typically 1m to 1000m). They can be made to have a standardised scale and shape, which can maximize sphere distribution to the same target spot, a greater interface region, which makes for more medicinal coatings and a faster rate of degradation and ion release and they can be designed to have a precise size and shape in many instances.

Drug Profile (Repaglinide)

Repaglinide is an oral hypoglycemic agent and first member of meglitinide class, used to treat type-2 diabetes mellitus. It blocks the ATP dependent potassium channel to stimulate release of insulin by binding to specific site on pancreatic b-cells. Repaglinide requires frequent dosing before meals due to short half-life and there by imposing side effects such as skeletal muscles pain, headache and giteffects. [1]

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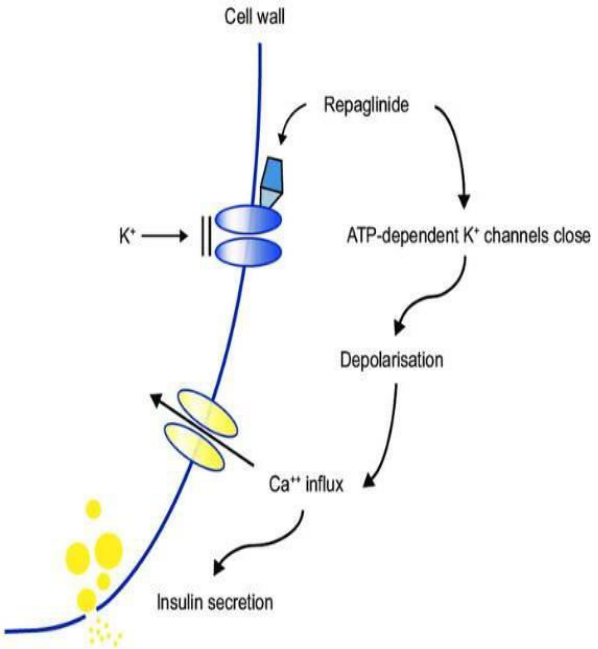
Repaglinide was the first meglitinide equivalent to be licenced as medicinal help worth in adults with T2DM.Repaglinide (Prandin) was formed as insulin secretagogues that works quickly and has a brief half-life. It's used to treat type 2 diabetes (1hr for repaglinide).Repaglinide is the S(+) enantiomer of 2-ethoxy-4-((3- methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acidand have a molecular weight of 452.6 Da .



Mode of action of repaglinide

Repaglinide is readily consumed after oral administration. The drug reaches its highest plasma concentration 30-60mins after controlling, plasma quantity quickly decreases and the drug is removed within 4-6hrs.Food has little effect on its absorption; it has a bioavailability of 63 percent and duration of 1hr.

Material and Methods

Chemicals used:-PLGA50:50, PolyvinylAlcohol, Potassiumdihydrogen Phosphate, SodiumHydroxide, SodiumAcetate, Ammoniumacetate, Dichloromethane, Methanol, Ethanol, Acetone, Potassiumchloride, Formaldehyde, Sodiumchloride, Diethylether, EDTA, Potassiumbromide(IR Grade), Isopropylalcohol.

Method:-

Preparation of 10% polyblend solutions

The polyblend between PLA and PCL was prepared with given composition. The polymers were completely mixed in dichloromethane and stirred for 30 min to obtain the polyblend solutions.

Formulation of Blend Microspheres

The preparation ofRepaglinide microspheres employed a modified solvent evaporation technique, a well-established method in pharmaceutical formulation. The process commenced with the emulsification of five milliliters of a polyblend solution in a 100 mL polyvinyl alcohol (PVA) solution with varying concentrations. The choice of PVA concentrations influenced the microsphere characteristics and drug release kinetics, an essential consideration in controlled drug delivery systems.

The emulsion underwent stirring at different revolutions per minute (rpm) for 15 minutes, affecting the droplet size and distribution within the emulsion. Control over these parameters is crucial as it influences the uniformity and encapsulation efficiency of the microspheres.

Subsequently, the resulting emulsion was introduced into 500 mL of distilled water, initiating the phase separation process. The stirring during this phase played a pivotal role in enhancing the microsphere formation. It allowed for the complete dispersion of the emulsion in the aqueous phase, leading to the creation of microspheres. Additionally, stirring for an additional 15 minutes influenced the homogeneity of the microspheres.

The critical aspect of this technique was the one-hour duration of continued stirring, primarily aimed at the complete evaporation of dichloromethane, a volatile solvent. The removal of this solvent ensured the safety and effectiveness of the final Repaglinide microspheres for pharmaceutical applications. Furthermore, the controlled evaporation played a pivotal role in achieving the desired microsphere size and drug loading capacity.

Following the evaporation process, the formed microspheres were meticulously collected by filtration. This step was crucial in isolating the microspheres from the surrounding solution, thus separating the product from any residual components.

To ensure the purity and safety of the Repaglinide microspheres, they underwent thorough washing with distilled water. This step effectively removed

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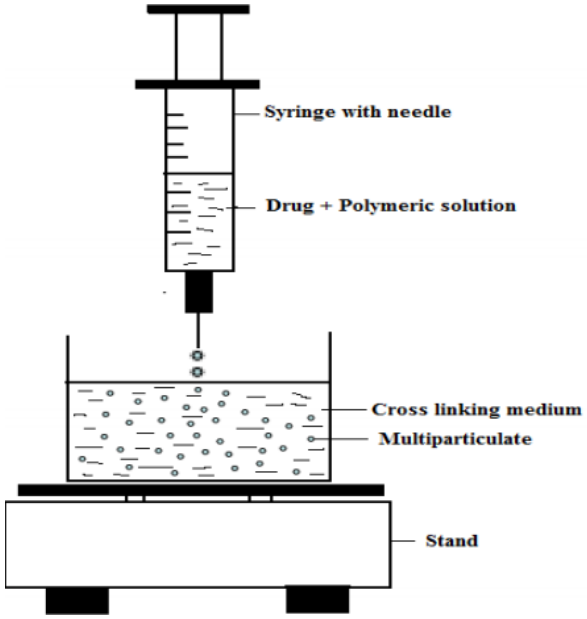
any residual solvents or impurities that may have adhered to the microsphere surface during the fabrication process.

Finally, the microspheres were subjected to drying in an oven, a critical step for eliminating any remaining traces of moisture. The moisture content in microspheres can impact their stability and shelf life, which is particularly significant in pharmaceutical applications .



***P*reparation of microsphere**

Physical evaluation :- It refers to the evaluation by sensory characters- color, odor, texture of the drug, etc.

Flow properties: In terms of the angle of repose, the Carrs index, and the Haussner ratio, the flow characteristics of powder were described. The mixture was poured through the walls of a funnel that was set such that its lower tip was exactly 2.0 cm above a hard surface in order to measure the angle of repose (θ).Bulk density is the ratio of the weight of powder to the volume it occupies. Bulk density is important in determining the size of the equipment needed for handling and processing.

Solubility: Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N HCl, 0.1N NaOH, Chloroform) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature.

Melting point: -It is one of the criteria used to assess the drug's purity. If pure chemicals occur, their melting points are precise and constant. The drugs are depicted with a specific range of melting point since they comprise a mixture of ingredients.

FTIRSpectroscopy :- The infrared spectrum is a significant record that provides adequate details on a compound's structure. This method produces a spectrum with a significant number of absorption bands, from which a wealth of knowledge about the structure of an organic chemical can be gathered. Near infrared is the zone between 0.8 and 2.5 microns, and far infrared is the region between 15 and 200 microns.The dried samples were homogenously mixed with potassium bromide and the mixture was then compressed into discs by a hydraulic compressor through applying pressure of about 10 tones in 2 min. The discs were placed in infrared light pass and the infrared spectrum was recorded in region of 400–4000 cm −1 using a FTIR spectroscope.

Determination of λ max of Repaglinide :- The λmaxofRepaglinide was identified by putting the drug solution's spectrum through a double-beam UV spectrophotometer. Procedure: 10 mg of the medication, which was precisely weighed, were dissolved in 10 ml of 0.1 N HCl solution in a volumetric flask.. The resulted solution (1000µg/ml) was used to prepare the concentration 10µg/ml. Using a UV spectrophotometer, the spectra of this solution was captured in the 200–400 nm region.

In vitro drug release from microspheres :- The drug release was performed in 0.1 N HCl for Repaglinide loaded microsphere. The drug release was performed in 0.1 N HCl (pH 1.2) for prepared microsphere using dialysis bag technique. In this study suspension of microsphere equivalent to 20 mg of microsphere was taken in dialysis tubing (MWCO, 15KDa, himedia) and placed in a beaker containing 50ml of PBS pH 7.4. The dialysis bag retains microsphere and allows passing of free drug into the dissolution media. Temperature was maintained at 37±10C throughout the study. The samples were withdrawn after specified time intervals that are 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 12hrs and replaced with the same volume of fresh

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0.1 N HCl and analyzed for drug concentration by using developed UV method.

Stability studies for optimized formulation :- Stability study data was revealed that the optimized microsphere formulation (F2) stable after 3 month of storage at 4ºC while at 25-28±2°C, the formulation was found unstable. Stability of formulation was observed on the basis of % EE, average particle size and physical appearance.

Results and Discussion

List of Sensory characters

1.	Color	Whitepowder
2.	Odor	Odorless
3.	Appearance	Finepowder

Solubility of Repaglinide

S.No.	Solvent	Solubility
1.	Water	Slightlysoluble
2.	0.1NHCl	Soluble
3.	0.1NaOH	Slightlysoluble
4.	Ethanol	FreelySoluble
5.	Methanol	FreelySoluble
6.	Chloroform	Sparinglysoluble

Melting point

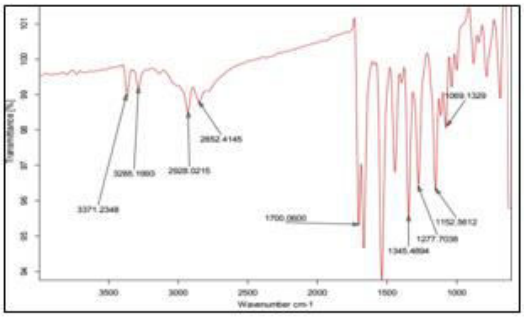
Melting point was determined by Differential scanning calorimetry (DSC). The melting point of repaglinide was found to be 126ºC.

Flow properties of Repaglinide

S.no	Parameter	Repaglinide
1.	AngleofRepose	43.05º
2.	Carrsindex (%)	32.173
3.	Bulk Density	0.345
4.	TappedDensity	0.456
5.	HausnersRatio	1.321

Interpretation of FT-IRSpectra

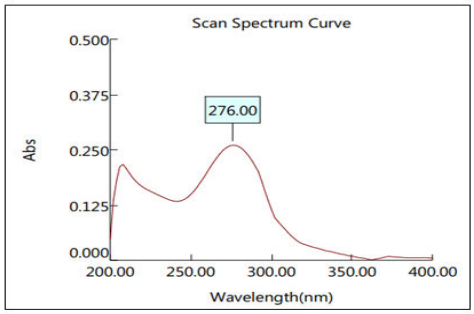
S.No.	PeakPosition	Interpretation
1.	3371.2348cm^{-1}	NHstretching
2.	2928.0215cm^{-1}	CHstretching
3.	1700.0600cm^{-1}	C= Ostretching
4.	1069.1329cm^{-1} and 1277.7038 cm^{-1}	C–Ostretching



FTIR of Repaglinide

U.V.Spectra ofPureDrug(Repaglinide)

Λmax of Repaglinide was found 278nm.



***In vitro* drug release for microspheres**

S.NO	Dissolution medium	Time (hrs)	Plain drug	% cumulative drug release F2
1.	SGF (pH 1.2)	1	43.32	13.45
2.		2.	65.85	20.65
3.		3.	98.98	25.65
4.		4.		36.65
5.		5.		45.85
6.		6.		58.85
7.		7.		69.98
8.		8.		72.23
9.		9.		85.56
10.		10.		92.25
11.		12.		98.85

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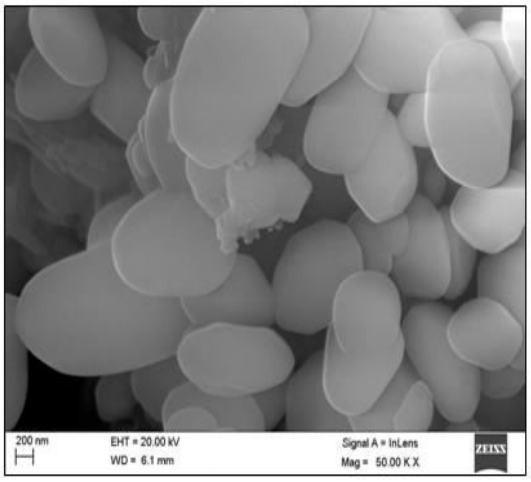
Characterization of stability study of Optimized formulation of microspheres F2

Characteristic	Time(Month)					
	1Month		2Month		3Month	
Temperature	4.0 ±0.2°C	25-28±2°C	4.0 ±0.2°C	25-28±2°C	4.0 ±0.2°C	25-28±2°C
Averageparticlesize (nm)	87.52±0.25	98.85±0.22	92.23±0.45	105.65±0.41	95.74±0.36	110.25±0.32
%EE	76.12±0.14	70.23±0.32	75.85±0.36	68.74±0.25	74.74±0.22	67.45±0.36

Conclusion

Controlled-release tablets are designed to release a drug in a predetermined and sustained manner within the body, often via biodegradation of the polymer matrix. The blend microspheres, in this context, serve as carriers that encapsulate the drug, facilitating its controlled release. Blending different polymers is a common technique used to modify and enhance the properties of polymer-based products. It offers a cost-effective alternative to developing entirely new products. Key factors that can be controlled or adjusted in the development of polymer blend microspheres include the molecular weight of the polymer, the composition of the blend, sphere porosity, size, and drug distribution. These factors play a pivotal role in determiningthe drug delivery profile.



SEM of Microsphere

The concept of polymer blends involves combining two or more polymer in to a single material, which offers the advantages of each individual polymer. Microspheres, on the other hand, are tiny spherical particles that find applications in controlled and sometimes targeted drug delivery systems. Their use enables the administration of medication in a manner that ensures a controlled rate of release. This approach has the potential to improve drug efficacy, patient compliance, and overall therapeutic outcomes.

In the context of Repaglinide, the development of controlled-release tablets using blend microspheres holds promise for addressing the challenge of frequent dosing associated with its short plasma half-life. The controlled and sustained release of Repaglinide from these tablets can enhance its therapeutic efficacy and patient convenience, offering a valuable contribution to diabetes management. This study's findings, particularly regarding the selection and optimization of polymer blends and microsphere characteristics important steps towards achieving this goal.

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