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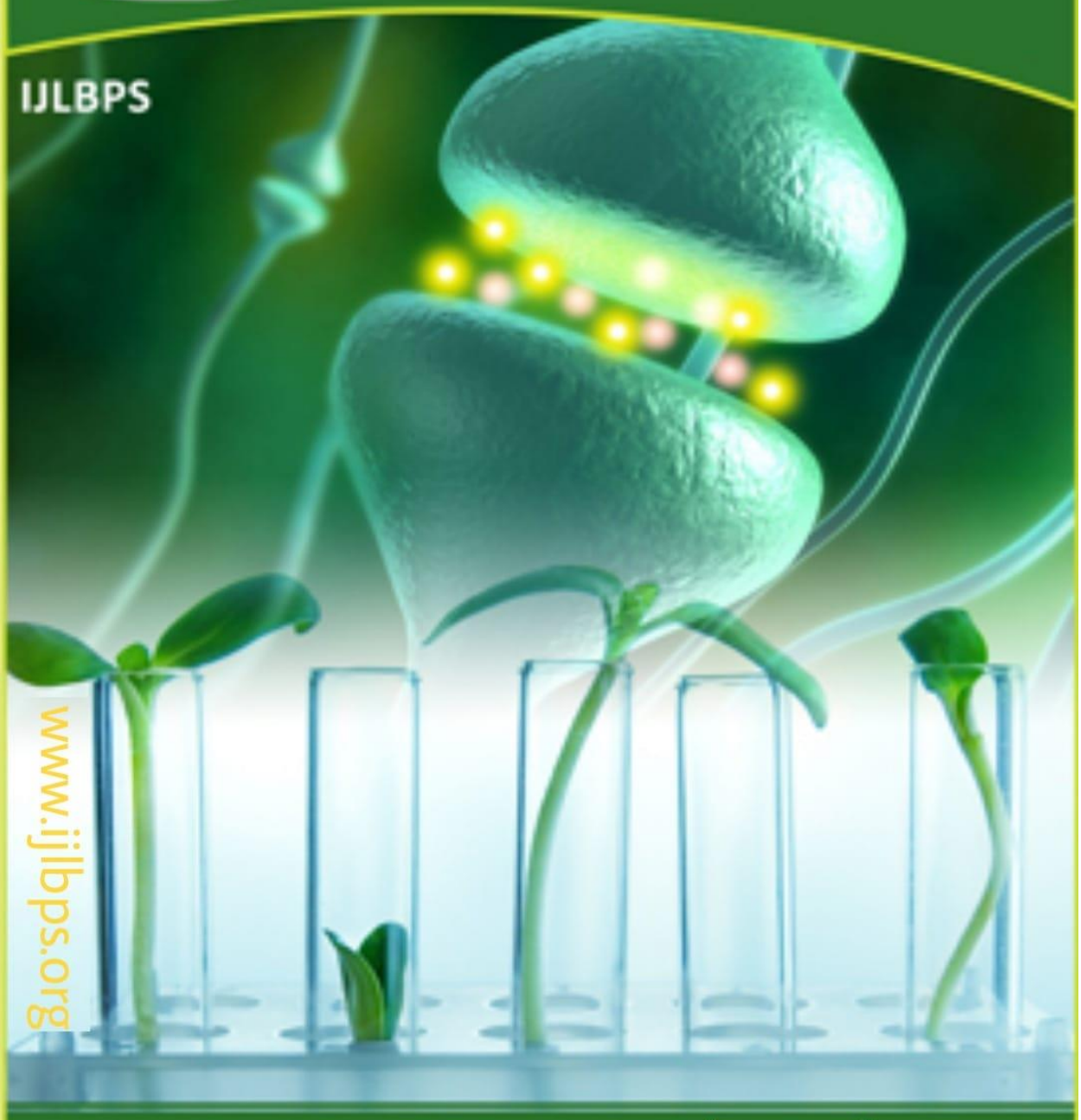

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Effect of various polymers on swelling and *in vitro* release oframipril in effervescent system

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Abstract

Tablet can be Utilized for precise delivery of drugs and reduce the drug concentrations at sites other than the target organ. The present study performed by preparation and evaluation of floating tablets of Ramipril as model drug. For prolongation of gastric residence time floating effervescent tablets were formulated by various materials like. hydroxypropyl methylcellulose (HPMC) K 4M, K 15M, K 100M and micro crystalline cellulose and gas generating agent like sodium bicarbonate and evaluated for floating properties, swelling characteristics and drug release studies. In vitro drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsemeyer Peppas equation. The drug release mechanism was found non-fickian type in most of the formulations. The developed floating tablets of Ramipril may be used in clinic for prolonged drug release for at least 12 h, thereby improving the bioavailability and patient compliance.

Key-Words: Ramipril, HPMC, Microcrystalline cellulose, Higuchi, Korsemeyer Peppas equation, Non-fickian

Introduction

Ramipril inhibit angiotensin converting enzyme (ACE) which is identical to KININASE II catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex, thus inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Thelatter decrease may result in a small increase in serum potassium. Ramipril have dose proportional over the
2.5 - 20 mg dose range. The absolute bioavailabilitiesof Ramipril were 28 %, when 5mg of oral Ramipril was compared with the same dose of Ramipril given intravenously.[1]Being weak acid PKa – 3.41, Ramiprilis well absorbed from the upper portion of the duodenum.[2]The aim of this work was to prepare and evaluate the Ramipril once daily sustained release tablets and to compare them with marketed products. Wet granulation method was adopted for the preparation of tablets using different retardant polymer excipients namely; hydroxypropyl methyl cellulose K4M/K15M/K100M, microcrystallinecellulose (pH 102), sodium bicarbonate, povidone (PVPK-30), isopropyl alcohol magnesium s t e a r a t e and talcum. The Controlled gartric rentention of solid dosage forms may be achieved by Mucoadhesion, [3] Floatation, Sedimentation and simultaneous administration of pharmacological agents.

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Gastrorententive floating drug delivery system (GRFDDS) has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the system. Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and inter-subject variability in plasma drug levels, effective for delivery of drugs with narrow Absorption windows, reduced dosing and increased patient compliance, reduced Cmax and prolonged drug levels above the minimum effective concentration, and improved safety profile for drugs with side-effects associated with high Cmax[4].

Material and Methods

Ramipril was received as a gift sample from Bal Pharmaceuticals Pvt. Ltd.Bengaluru, hydroxypropyl methylcellulose (HPMC K4M, K15M, K100M), microcrystalline cellulose (Avicel PH 101) were All other compounds were of an analytical standard.

The typical wet granulation procedure was used to make the tablets. The numerous excipients utilized were mentioned in Table 1(Effervescent System). Everything was completely combined and strained through a No. 60 sieve except the glidants and lubricant. PVP K30 (the binding agent) was dissolved in enough isopropyl alcohol (the granulating agent) to achieve the desired concentration before granulation. The wet mixture was strained through a No. 12 sieve and dried at 50 degrees Celsius for two hours. The dried granules were lubricated with magnesium stearate and talc and compacted into tablets using single station tablet punch machine with 8 mm cancave facing punches.5,6,7

Property that can float

Total floating time (TFT) refers to the length of time the dosage form continuously floats on the surface of the medium, whereas floating lag time (FLT) refers to the time it takes for the tablet to emerge on the surface of the medium. Measurements were taken of the buoyancy of each tablet formulation in a Dissolution device at 370.5 °C in 900 cc of 0.1N HCL (pH 1.2). Visual observation was used to determine the length of time spent afloat.8

Study of Water Absorption

The polymer's water-absorption capacity is a crucial factor in estimating its swelling. The tablets' WU was measured using a USP 24 dissolving equipment II. The conditions were 370.5 °C and 50 rpm, with the medium consisting of 900 cc of 0.1 HCl. Tablets were taken out at regular intervals, wiped to remove excess water, and then weighed.8 The pills' swelling properties were quantified in terms of their ability to absorb water.9

Weight Utilization Percentage = (Initial Tablet Weight - Final Tablet Weight) X 100 / Final Tablet Weight.

Drug release testing in vitro

Ramipril's drug release study was measured spectrophotometrically in 900 ml of 0.1 N HCL at 370.5°C while rotating at 50 rpm using a USP paddle dissolution equipment. Each time the medium was changed, a certain number of samples were taken at regular intervals. Sample absorbance was determined spectrophotometrically at a Wavelength of 210 nm. 10

Discussion and Results

The course of formulation was determined in part by the findings of a preliminary investigation to assess the compatibility of the medication excipients. Compatibility between the medicine and polymers was confirmed by IR spectroscopy (Figure 1), including spectra for Ramipril (3464.99 cm-1, 3280.72 cm-1, 936.52 cm-1, 2865.78 cm-1, 1743.35 cm-1, 1652.71 cm-1).

System with a lot of fizz

All effervescent tablets float on immersion in a 0.1 N HCL, pH 1.2 solution at 37 0.5 °C, and they maintain their buoyancy for at least 12 hours. Gas was produced by the addition of sodium bicarbonate. In the presence of the dissolving media (0.1N HCL), sodium bicarbonate caused carbon dioxide to be produced. The tablet's density drops below 1, making it float thanks to the gas contained and protected inside the gel created by the hydration of polymer (methocel).

Compared to formulations comprising high viscosity grade methocel K15M (42s) and K100M (60s), tablets containing low-viscosity grade methocel K4M displayed minimal floating lag time (25s). In vitro buoyancy was shown to be affected by the gel-forming polymer methocel's molecular weight distribution or viscosity.

An increase in HPMC concentration was discovered to function as a swelling agent, capable of expanding in the presence of a gastric fluid mimic. The drug release was shown to diminish after 1 to 2 hours when the HPMC concentration was increased from 40 mg, 60 mg, and 80 mg. Three distinct concentrations of each were developed. Despite the high viscosity grade, HPMC K100M had a satisfactory dissolving profile after 12 hours, outperforming HPMC K4M and HPMC K15M. Formulations with 40 mg, 60 mg, and 80 mg of HPMC were made to see how their respective concentrations affected drug release. The dissolution profile showed that the burst drug release and the release rate of drug after 12 hours were both reduced with increasing HPMC content. More gel is generated at higher HPMC concentrations. The drug's diffusion route is lengthened by this gel. Because of its viscosity, the drug's diffusion coefficient is altered. This results in less medication being secreted into the system.

Drug distribution analysis

We looked at the drug release data to see what kind of release mechanism was used. The best match with the greatest determination R2 coefficients was given by both the Higuchi and first order models followed by zero order which imply the drug release via diffusion process.

Diffusion, swelling, and erosion are the three most significant rate regulating mechanisms followed in controlled or sustained release formulations. Fickian diffusion best describes the mechanism of drug release from the polymeric system. But in case of formulations containing swelling polymers, other processes include relaxation of polymers chain, imbition of water causing polymers to swell and changing them from initial glassy to rubbery state. Due to swelling considerable volume expansion takes place leading to moving diffusion boundaries complicating the solution of Fick's second law of diffusion.

So to explore the release pattern, results of the *in vitro* release data were fitted to Korsmeyer Peppas

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Conclusion

Finally, we found that a mixture of microcrystalline cellulose and high-molecular-weight HPMC showed promise as a polymer for an effervescent gastroretentive drug delivery system. Swelling studies suggest high water intake and led to medication release and might be crucial in stomach retention. It was observed that drug release was diffusion regulated, and the formulations followed Higuchi kinetics. The newly designed Ramipril floating pills might be employed

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