



Formulation and development of floating microspheres containing levodopa and carbidopa

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ABSTRACT :- The main objective of work to develop long acting sustained release floating microballons of levodopa and carbidopa by emulsion-solvent evaporation technique for the treatment of Parkinson's disorder. All current levodopa products are formulated in combination with aromatic amino acid decarboxylase inhibitors such as benserazide to prevent the peripheral metabolism of levodopa. In the present research work was to produce floating microspheres of carbidopa and levodopa to enhance their efficacy by increasing their gastric retention time which is major technique to improve efficacy of narrow absorption window drugs, and its improved bioavailability. The effect of various formulation were evaluated and process variable on the particle size, in vitro floating behavior, percentage yield and in vitro drug release were studied. Further, the microspheres could also be compressed in to tablets, filled in to capsule or formulated in to oral suspension for reconstitution.

KEY WORDS: - HPMC K15M, EC, Emulsion-solvent evaporation technique, Parkinson's disorder.

I. Introduction :-

Parkinson's disease is a progressive, neurodegenerative disorder of the extra pyramidal nervous system affecting the mobility and control of the skeletal muscular system. They include resting tremor, rigidity and bradykinetic movements, symptomatic treatments such as levodopa therapies may permit the patient better mobility.

Levodopa is a primary drug used in the treatment of Parkinson's disorder. All current levodopa products are formulated in combination with aromatic amino acid decarboxylase inhibitors such as benserazide to prevent the peripheral metabolism of levodopa. Orally administered levodopa causes variable and unvariable clinical responses because of its erratic oral absorption and first-pass metabolism. The oral bioavailability of levodopa alone is estimated at about 5% and less than 1% of the orally administered dose reaches the brain.^[1,2]

Carbidopa inhibits decarboxylation of levodopa by a patient's body tissues outside of the brain. Small dose of carbidopa administered in conjunction with levodopa allow a larger percentage of levodopa to reach the brain unchanged for later conversion to dopamine and allows for lower doses of levodopa with a concordant reduction of side effect.

Gastroretentive drug delivery system (GRDDS) can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment that have narrow therapeutic window, by this way they prolong dosing interval. It has applications also for local drug delivery to the stomach and proximal small intestines.^[3]

The floating microspheres beneficially alter the absorption of a drug, thus enhancing its bioavailability. They prolong dosing intervals which would allow development of once a day formulations and thereby increase patient compliance beyond the level of existing dosage forms by achieving control over gastric residence time. Floating microspheres are gastroretentive drug delivery systems based on a non-effervescent approach. These microspheres are characteristically free-flowing powders having a size $< 199\mu\text{m}$ and remain buoyant over gastric contents for a prolonged period. As the system floats over gastric contents, the drug is released slowly at the desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.^[4,5]

The rationale behind this study was to formulate and develop floating microspheres of levodopa and carbidopa by emulsion-solvent evaporation technique for the treatment of Parkinson's disorder and enhance their efficacy by increasing their gastric retention time which is major technique to improve efficacy of narrow absorption window drugs, and its improved bioavailability.

II. Materials and Methods:

Material:-

Levodopa and Carbidopa was obtained from Hetro Pharmaceutical Pvt. Ltd,Hydrabad,India as a gift sample. HPMC K15M and EC were procured from Ponmani labs, Coimbatore,India. Dichloromethane, Ethanol, Tween 80 were procured from S.D. Fine chemicals Ltd. Mumbai, and were of all other reagent and solvents of analytical grade.

Methods :-

Preparation of Floating Microspheres of levodopa and carbidopa:

Floating microspheres were prepared by o/w emulsion solvent evaporation method.^[6,7] (Fig no 1). Weighed amount of drug was mixed with polymers in ratios of (1:1, 1:2 and 1:3) in a mixture of Dichloromethane and Ethanol (1:2) at room temperature. and the preparation was stirred at 500 rpm with a three- blade propeller (Remi, Mumbai) for three hour to obtain o/w emulsion. At low agitation speed, the size of the microspheres increased due to agglomeration of microspheres and generation of surface charge and also formation of microspheres due to which buoyancy decreased, but an increase in agitation speed resulted in reduction of microspheres size. The formed floating microspheres were passed through sieve no.18, 30 and washed with water and dried at room temperature in desiccators.^[7,8]

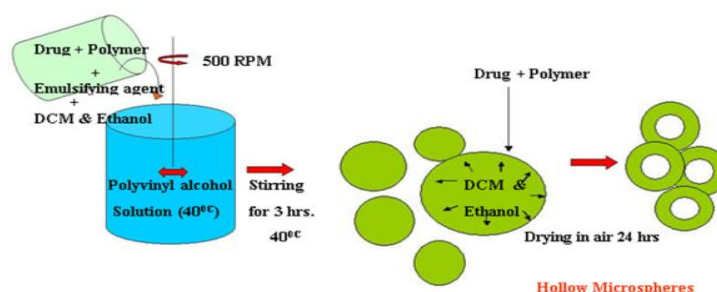


Fig No :1 Mechanism of formation of floating microspheres by emulsion solvent Evaporation method

III. Results:-

Floating microspheres of Levodopa (LD) and Carbidopa (CD) were prepared and evaluated from preformulation studies like melting point, FTIR, UV, Spectroscopy and solubility analysis. Maximum solubility was found in 0.1 M HCL. The melting point of drug was found to be Levodopa and Carbidopa in the range of 281^{OC} to 207^{OC} respectively.

The compatibility evaluations were performed by Fourier transforms infra-red spectroscopy studies which showed that polymers and drug were compatible with each other. There was no interaction found between polymer and drug. The floating microspheres are significantly increased with increasing ethyl cellulose of exhibited a particle size of (479.14 ± 02.45µm). The optimized formulation displayed better buoyancy of LD (74.43 ± 3.46%), CD (78.16 ± 4.32%) and percentage yield LD (78.30± 0.33%), CD (72.34 ± 0.33%) respectively. This optimum formulation was subjected to the *In vitro* drug release dissolution apparatus USP type II. It was found that the optimized batch of floating microspheres of drug released at the end of 12 hrs. This shows that hollow microspheres provide a sustained release of drug in the GIT and remain floated for more than 12 hrs.

IV. Discussion:-

In vitro data obtained from floating microspheres of levodopa and carbidopa showed excellent floatability, good buoyancy, and prolonged drug release. The design system microspheres floats in the stomach and prolongs the gastric residence time (GRT) consequently, providing sustained released action. In addition, hollow microspheres enabled increased drug absorption rate, as it gradually sank in the stomach and arrived at the absorption site.

The main objective of work to develop long acting sustained release floating microballons of levodopa and carbidopa with a polymers HPMCK15 and EC in different ratio prepared by emulsion-solvent evaporation technique were optimized and the performance of these formulation was evaluated for the treatment of Parkinson's disorder.

Floating microspheres were selected for the design of a gastro-retentive floating drug delivery system with a view to improve the drug of oral bioavailability. The sustained release of floating microspheres to provide a convenient dosage form for achieving best performance regarding flow, drug entrapment, and drug release. Further, the floating microspheres could also be compressed in to tablets, filled in to capsules or formulated in to oral suspension for reconstitution.

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