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Comparative evaluation of HPMC K100 and poloxamer 188 - influence on release kinetics of Curcumin in floating microspheres

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ABSTRACT

The present investigation involves formulation and evaluation of floating microspheres with curcumin as model drug for prolongation of gastric residence time and to evaluate the influence of polymers on the release kinetics. The microspheres were prepared by oil in water (o/w) emulsion / solvent evaporation method using HPMC K100 and Poloxamer 188. Characterization of microspheres followed, to examine the size of microspheres, drug incorporation efficiency, % yield, buoyancy percentage and *in vitro* drug release. Drug release kinetics was evaluated using linear regression method. The influence of the agitation speed during preparation, polymer concentration, solvent proportion and dissolution medium on the size of the microspheres and drug release were discussed. The prepared microspheres exhibited prolonged drug release (~10h) and remained buoyant for ~ 12 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. Agitation speed showed minimum significance on drug release profile. *In vitro* studies demonstrated diffusion controlled drug release of curcumin from the microspheres. Through the study, the developed curcumin loaded floating microspheres could be used as a drug delivery system to improve the absorption kinetics of curcumin. Poloxamer 188 may be further evaluated for claiming the *in vivo-in vitro* correlation.

Keywords: Curcumin, Drug delivery system, Blends, Hydrophilic Polymers, kinetics.

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INTRODUCTION

Many different kinds of sustained drug delivery systems have been proposed for various routes of administration, since they require less frequent drug administration, provide more therapeutic effects, and reduce the incidence of side effects. To develop a drug delivery system for oral administration, the preferred route of administration, it is necessary to optimize not only the release rate from the system but also the residence time of the system in gastrointestinal tract [1]. Various oral delivery systems have been developed including osmotic tablets, polymeric matrices and microcapsules. However, limited number of approaches has been pursued to extend the residence time of the delivery system within the GIT. Floating drug delivery system (FDDS) or Hydrodynamically Balanced System (HBS) are among the several approaches that have been developed in order to increase the gastric residence time (GRT) of dosage forms [2-4]. Single unit systems possess a disadvantage of "all or nothing" effect leads to high intersubject variability [5, 6]. Still the multiple unit dosage forms may be better suited because they are claimed to reduce the intersubject variability in absorption and lower the probability of dose dumping [7,8]. Development of floating delivery system involves use of many low density polymers. HPMC is one such low density polymer. Many controlled release dosage forms utilize hydrophilic polymers for retarding drug release. The mechanism of drug release is dependent on the swelling and dissolution process. In this case the early part of the release process is marked by swelling due to conversion of the polymer from a glassy to a rubbery state due to water penetration. Poloxamer 188 is a poly (ether) with a molecular weight of around 8300, containing about 80% poly (ethyl oxide) segment and 20% poly (Propyl oxide) segment low density polymer. The Poloxamer 188 is a surfactant which may be used as a pore forming agent. Previous studies suggests that the rate of release of drugs from the Poloxamer 188 found to have controlled release kinetics [9] which can be utilized for achieving the floating device with controlled release profiles.

Curcumin is a potent phytomolecule with wide range of biological activity [10, 11] possess a low absorption [12]. It is poorly absorbed in the lower GIT and has short elimination half life ~0.39 h. The object of the present investigation was to formulate floating microspheres of curcumin in order to achieve a prolonged retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The prepared microspheres were evaluated for size, *in vitro* release, and buoyancy and incorporation efficiency. The effect of various formulation variables on the size and drug release was studied.

MATERIALS AND METHODS

Curcumin was purchased from Sigma Aldec German. HPMC K100 and Poloxamer 188 purchased from SD fine chemicals, Mumbai. All other materials were of analytical grade.

Preparation of microspheres

Microspheres with an inner hollow structure were prepared by oil in water (o/w) emulsion / solvent diffusion method. The polymer is dissolved in an organic solvent and drug is dissolved / diffused in polymer solution. The solution containing drug is then emulsified in an aqueous phase containing PVA to form o/w emulsion. The emulsion is stirred subsequently at ranging agitation speed for 30 min to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried in vacuum desiccator.

Characterization

The size of microspheres was determined using a light microscope fitted with an eye piece micrometer calibrated with stage micrometer.

Buoyancy percentage

Microspheres 300mg were spread over the surface of USP XXIV dissolution apparatus (TYPE II) filled with 900 ml of 0.1 mol L^{-1} HCL containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The

microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

Incorporation efficiency

To determine the incorporation efficiency microspheres were taken, thoroughly triturated and suspended in a minimal amount of alcohol. The suspension was suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically at 430nm.

In vitro release studies

A USP basket apparatus has been used to study *in vitro* drug release from microspheres. In the present study drug release was studied using a modified USP XXIV dissolution apparatus type I (basket) at 100 rpm in distilled water and 0.1 mol L^{-1} HCL (pH 1.2) as dissolution fluids (900ml) maintained at $37^0C \pm 0.5^0C$. Samples withdrawn at periodical intervals and analyzed spectrophotometrically at 430 nm. The volume was replenished with the same amount of fresh medium to maintain the sink condition. All experiments were performed in triplicate. Linear regression was used to analyze the *in vitro* release mechanism.

RESULTS AND DISCUSSION

Floating microspheres were prepared by oil in water (o/w) emulsion / solvent diffusion method using HPMC K100 and Poloxamer 188. The average size distribution of floating microspheres found to be in the range of 101 to 220 micrometer. The prepared microspheres floated for prolonged time over the surface of the dissolution medium. Buoyancy percentage of the microspheres was found to be in the range of 70.2 to 90.2%. Microspheres were prepared using HPMC K100 and Poloxamer 188 with varying concentrations (10% – 40%) and subjected to various formulation variables evaluation. The mean particle size of the microspheres significantly increased with increasing polymer concentration and was in the range of 101± 2.8 to 220± 3.6 micrometers. The viscosity of the medium increases at higher polymer concentration resulting in enhanced interfacial tension, shearing efficiency is also diminished at higher velocities [13, 14] this results in the formation of larger particles. It is obvious that the agitation speed affect the yield and size distribution of microspheres. The size of the microspheres decreased with increasing agitation speed. *In vitro* curcumin release studies were performed in 0.1mol L^{-1} HCL for 8 hrs. The cumulative release of curcumin significantly decreased with increasing polymer concentration. The increased density of polymer matrix at higher concentrations results in an increased diffusional path length. This may decrease the overall drug release from the polymer matrix. No significant effect of solvent composition was observed on the *in vitro* release. Poloxamer 188 blend low concentration 10% showed nearly 40% of drug release within 12 hours. The microspheres drug loading capacity for 10% Poloxamer 188 blend microspheres was found to be 37.5%. Poloxamer 188 is amphiphilic surfactant which is soluble in both water and organic solvent. The low density nature of Poloxamer is made the formulation to float for prolonged period which may facilitate the absorption kinetics by facilitating the rate of release of curcumin due to its pore forming nature. Studies using Poloxamer 188 suggests that the amphipathic nature of the Poloxamer 188 acts at interface of the lipid membranes and forces the lipid molecules more tightly. On the other hand studies [13-15] reveals that curcumin binds to the interface of the lipid bio membranes and higher dose is required to get partitioning into the lipid bio membranes. The drug diffusion process is the key factor to determine the drug release from the blend microspheres. The amphipathic nature of Poloxamer 188 also one of the reason to improve the solubility of curcumin in the intestinal membrane to improve the absorption of curcumin. As for the drug diffusion process, concentration difference in HPMC matrices was the driving force to allow the drug to diffuse out from the microspheres.

CONCLUSION

To conclude, curcumin absorption and kinetic parameters can be modified by formulating as floating drug delivery system. To achieve optimized release kinetics hydrophilic polymers like HPMC and Poloxamer can be used for the development of microspheres. The Poloxamer / curcumin blend found to undergo controlled release while compared to HPMC based curcumin microspheres. The concentration of the polymer can be kept low to achieve controlled release profile. Formulation variables such as agitation speed and

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Table 1. Various formulation parameters for microspheres

Formulation	% Yield	Particle Size[a] (µM)	Drug Content in 100mg[b]	Buoyancy % [b]
HPMC 10 %	84.6	101 ± 2.8	24.75 ± 2.3	82.5 ± 2.8
HPMC 15%	70	149 ± 4.8	15 ± 1.2	90.2 ± 4.8
HPMC 20%	75	190 ± 6.2	22 ± 2.2	84.2 ± 1.2
HPMC 30%	43.5	178 ± 2.7	9.25 ± 1.8	78.5 ± 5.5
HPMC 40%	36	220 ± 3.6	8.75 ± 1.8	74.2 ± 2.3
Poloxamer 10%	85	120 ± 5.9	37.5 ± 1.3	89.2 ± 1.2
Poloxamer 15%	66.6	138 ± 3.3	25.75 ± 1.5	90.3 ± 3.2
Poloxamer 20%	48	158 ± 5.8	20 ± 1.1	80.1 ± 4.8
Poloxamer 30%	45	158 ± 6.7	19 ± 1.9	87.1 ± 2.2
Poloxamer 40%	70	168 ± 6.3	15 ± 2.9	83.7 ± 2.2

a, b – Triplicate

solvent composition is not having a significant effect on the release profile of the floating microspheres. While compared to HPMC based curcumin microspheres the Poloxamer based curcumin microspheres shows a controlled release kinetics which may be further evaluated with use of *in vivo* animal studies followed by *in vitro* and *in vivo* correlation.

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Fig 1: *In Vitro* dissolution studies for the curcumin loaded microspheres with different concentrations of HPMC

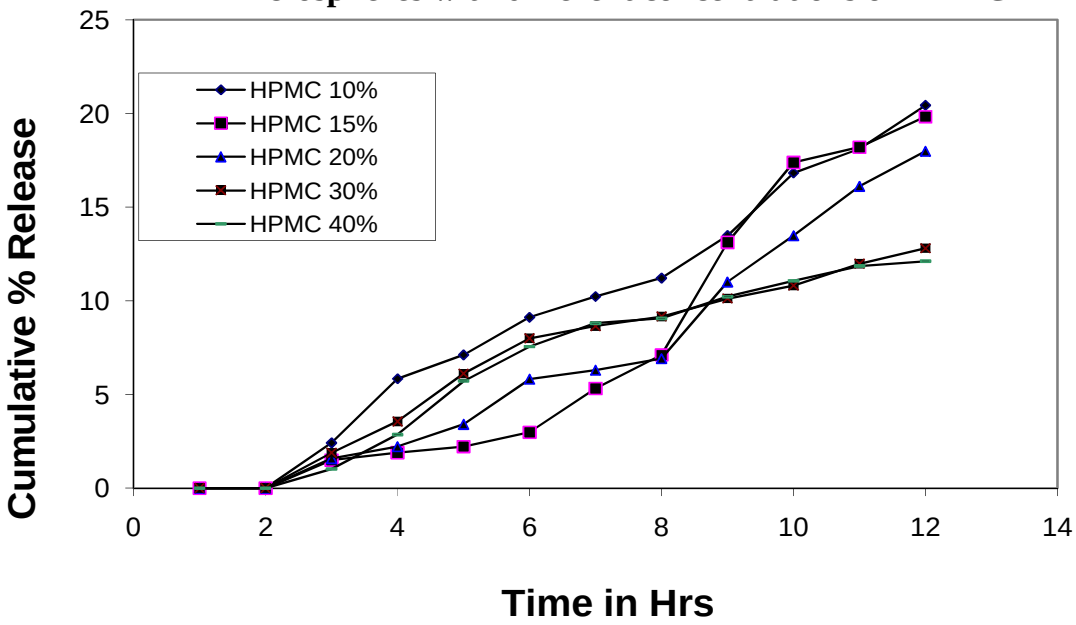

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Fig 2: *In vitro* dissolution studies for the curcumin loaded microspheres with different concentrations of Poloxamer 188

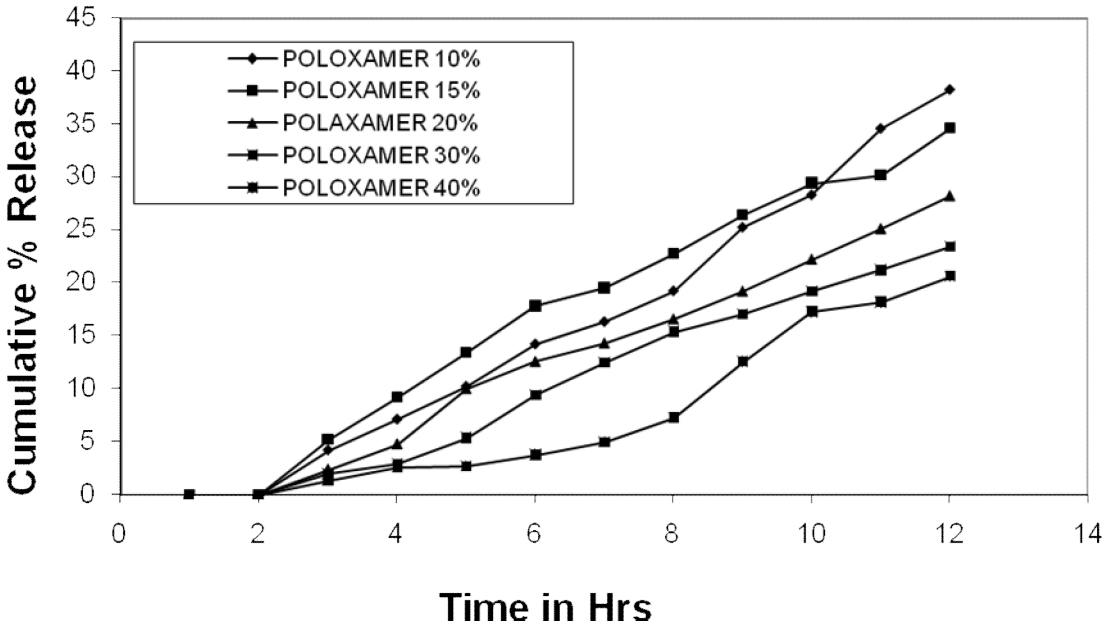

Fig 3: In vitro dissolution release comparison of curcumin loaded HPMC blend with curcumin loaded Poloxamer 188 blend microspheres.

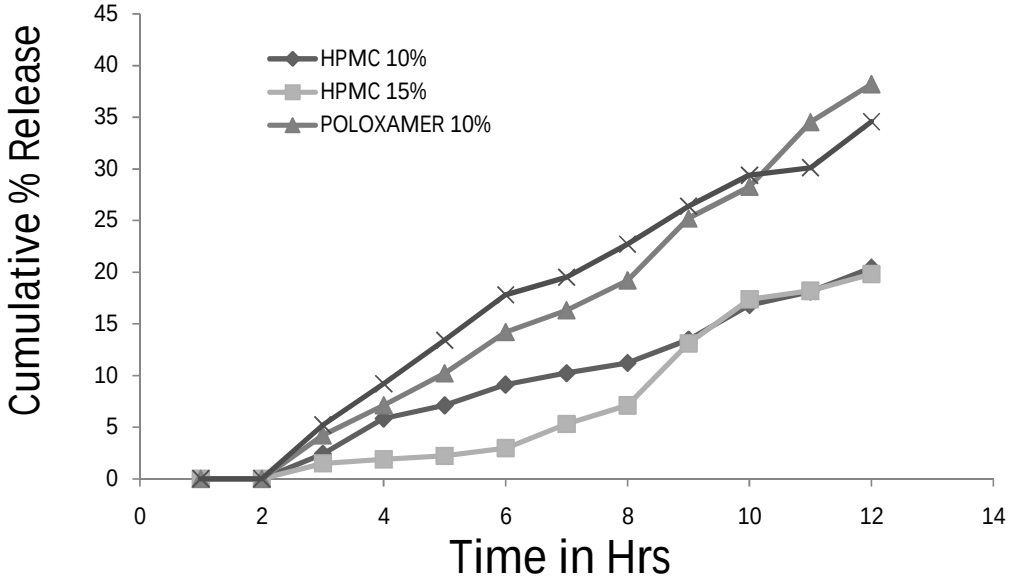

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Fig 4: Effect of Agitation Speed on Dissolution Profile

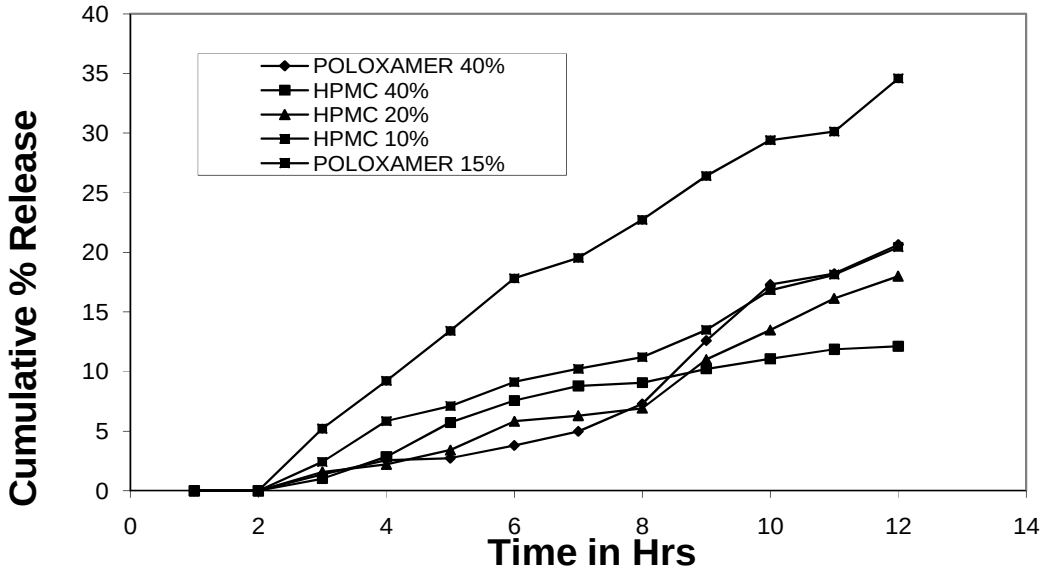
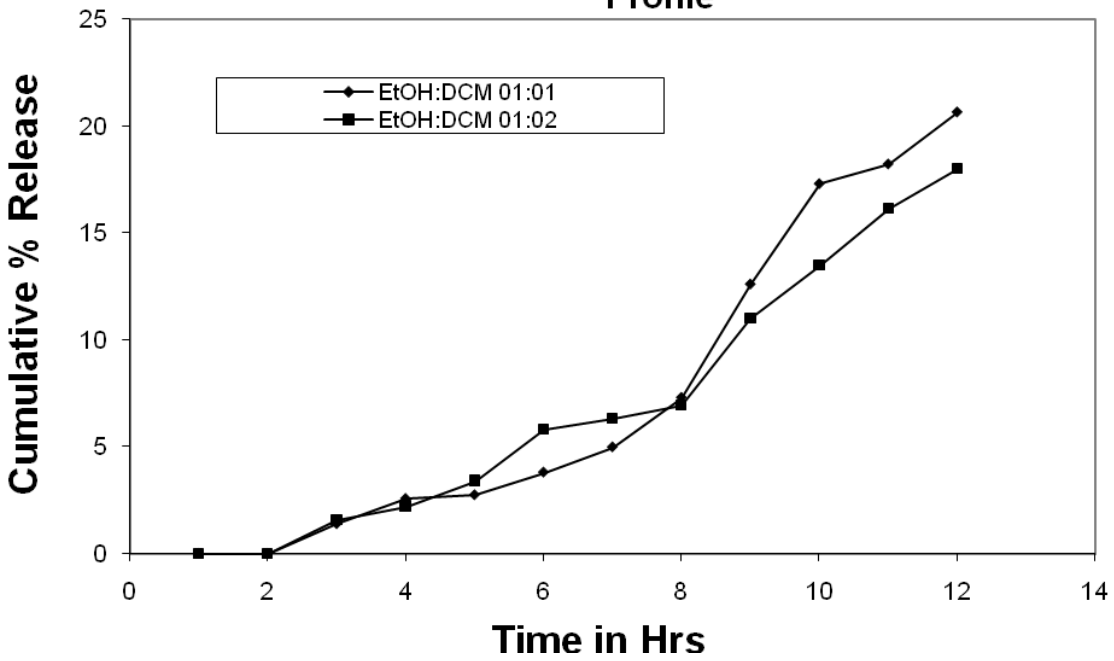


Fig 5: Effect of Solvent Composition On Dissolution Profile



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