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GASTRO FLOATING HYDROGELS AS NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Introduction: Novel Drug Delivery System (NDDS) is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. NDDSs cure a particular disease by targeting the affected zone inside the patient's body and transporting the drug to that area. Floating Drug Delivery Systems (FDDS) are novel systems that have a bulk density lower than the gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for an extended period. Gastro floating hydrogels can be used in drug delivery systems due to both gelling unique properties and floating in stomach fluids. **Materials and Methods:** Gastro floating hydrogels of Clarithromycin (CM) were formulated and prepared with different polymers such as: Carbopol, HPMC, MCC, and PEG. The floating time in the acidic fluid was calculated, and the drug release profiles in the acidic medium were obtained and studied. **Results and Discussion:** The optimal formula floated after 0.9 minute in contact of the acidic fluid, and both floating and drug release profiles showed extended release of CM and nearly complete release (98.5%) after 20 hours of the study.

KEYWORDS: Drug delivery systems, Traditional drug, Gastro floating hydrogel, Carbopol, Clarithromycin, HPMC, acidic fluid, extended release.

INTRODUCTION

Every drug is formulated in a pharmaceutical dosage form that is composed of one or more active pharmaceutical ingredients (APIs) and one or more inactive pharmaceutical ingredients, which called excipients (Exp). APIs are the components used to treat and diagnosis diseases, while excipients are used to give the optimal formulation, to protect and to improve APIs efficacy, and make the drug manufacturing process easier.[1]

Dosage forms can be administered through different routes based on the target site, duration of treatment and the physicochemical attributes of the drug. The most common route is the oral route, because of the ease of administrating and the simplicity of manufacturing. Some of the conventional oral dosage forms are tablets, capsules, pills, and syrups. Other routes of drug administration are less important, however, they are commonly used when we can't use the oral route as in vomiting or if the drug is instable in the gastric fluids. An example of these routes is the dermal route which can be applied in conventional dosage forms such as ointments, gels, creams, and pastes. Another example is the Parenteral route administrated in conventional dosage forms such as ampoules, vials, and serums.[2]

Drug Delivery is the method of administrating and releasing the pharmaceutical ingredients to achieve a therapeutic effect in humans or animals, whereas Drug Delivery Systems (DDS) describe formulations, devices, technologies and systems that transport drugs into or throughout the body, and release them as needed doses, for providing an accurate therapeutic amount of active pharmaceutical ingredients and improving safety and efficacy by controlling the location, rate, and time of release in the body.[3,4] A number of DDS are currently under investigation to get rid of problems commonly found in conventional dosage forms and to improve the potential of the respective drug. On the other hand, there has been a focus on the microenviron-ment of the cells and their interaction with these new dosage forms.[5] These new technologies, as nanotechnology, have prompted the old concept of the magic bullet proposed by the scientist Paul Ehrlich's vision.[6] Now a days both Nano medicine and Nano Delivery Systems are developing rapidly where materials in the nanoscale range are employed in medical and pharmaceutical applications and could serve as diagnostic tools or to deliver APs to defined targeted sites in a precise manner,[7] as for cancer treatment,[8] or for Alzheimer and epilepsy treatment.[9,10] Hydrogels can be used also as novel DDS. Hydrogels are cross-linked polymers with hydrophilic groups, which enable them to absorb large amounts of water.[11] Although hydrogels have numerous capabilities and advantages in drug delivery including biocompatibility, low toxicity, and good swelling behavior, but the drug release from hydrogels depends on many factors, such as polymers properties especially swelling properties, mechanical strength, and environmental conditions as temperature, electrical ions, and Ph.[11] Polymers which are used in hydrogel preparation could be from natural or synthetic sources. Each of these types of polymers should be selected according to the hydrogels mode of administration and the target site of drug action. Polymers might be cross-linked through chemical or physical reactions or through ionizing radiation

methods.[12,13] Hydrogels, called sometimes smart hydrogels have a lot of applications in drug delivery systems. They can be employed for topical treatment as for treating acne vulgaris,[14] or for leading to expansion in the anti-inflammatory and pain relief use of Resveratrol and Lornoxicam,[15,16] and for increasing therapeutic effects of APIs, as for Kaempferol (Antioxidant flavonoid) while the efficacy was noticeably increased in hydrogel formulation.[17] Another important example of DDS is Floating Drug Delivery Systems FDDS or hydro dynamically balanced systems. FDDS are modern systems that form in contact with the gastric fluid a sticky structure which has a bulk density lower than the gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate, and stay in stomach for a extended period.[18] Floating systems are divided into effervescent systems (depend on gases) and no effervescent systems.[18] Gastro Floating Hydrogels (GFHs) as drug delivery systems can be used for many drugs due to both gelling unique properties and floating purposes, as for increasing therapeutic efficacy and decreasing side effects. A study carried out for Meloxicam (Non steroid anti-inflammatory drug) which formulated in gastro floating in-situ gel showed a significant reduction in local acidic ulceration potential compared to pure meloxicam, and the results of the drug release were high after 6 hours (77%).[19] GFHs are useful for drugs predominantly absorbed in stomach, such as Theophylline which was formulated in floating multi-layer coated tablets. (figure 1).[20] GFHs are also useful for Clarithromycin extended release in stomach.[21]

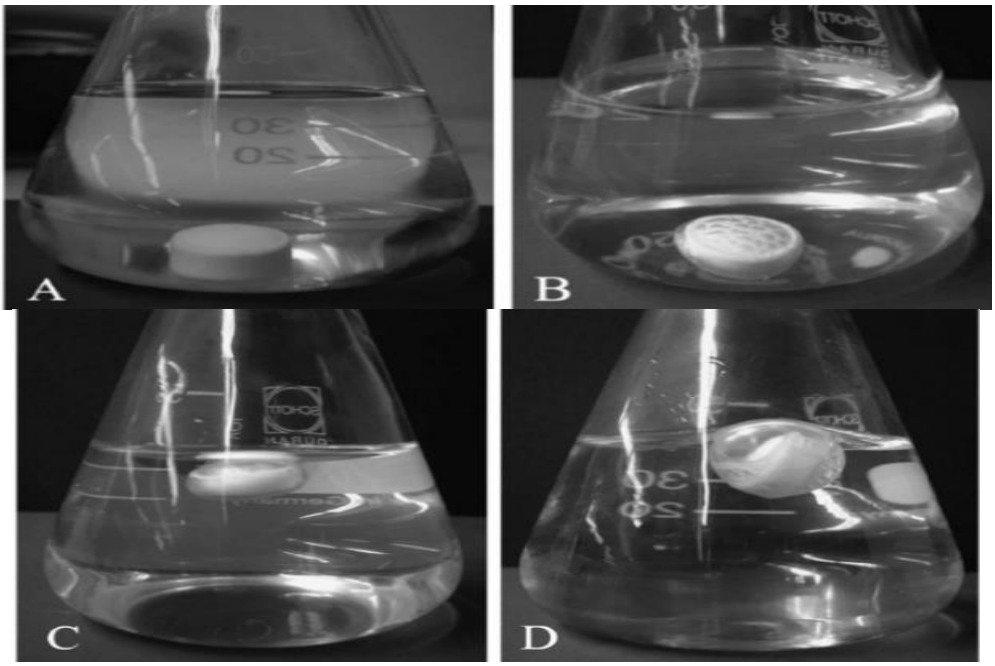

Figure 1: Floating sequence in 0.1 N HCl of a floating multi-layer coated tablet using direct compressed core (A: 0 min, B: 1 min, C: 4 min, D: 480 min).[20]

Clarithromycin (CM) is a synthetic antibiotic produced by the genera Actinobacteria and Proteobacteria.[21] It is used for the treatment and prevention of anaerobic microorganisms and protozoa infections. It is an active adjunct in the treatment of Helicobacter pylori which produces acidic mucosal irritation leading to inflammation.[22] CM is mainly absorbed in the stomach,[23] and is available as orally, intravenously, vaginally and rectally presentations, although the most clinically used is the oral presentation. Its oral dosage forms of 250 or 500 mg are rapidly absorbed and distributed almost to the entire body.[24] This study aimed to develop an Acidic Floating Hydrogel of Clarithromycin for *Helicobacter pylori* treatment using polymers of different compositions and properties, such as Carbopol, MCC, and HPMC. Drug release evaluation in vitro and floating properties estimation in the acidic medium were performed.

MATERIALS AND METHODS

Materials

Clarithromycin CM, Carbopol, HPMC, and Macrogol were purchased from Sigma- Germany. Ethanol and other excipients were purchased from Merck- Germany. All other chemicals and reagents were of analytical grade and used as received.

Methods

Preparation of CM Gel

Many gels formulations were prepared with different excipients, and different ratios of Drug: HPMC: Carbopol: MCC in purpose to make the floating process in acidic medium easier and more rapid.

The chosen formula was composed of: Carbopol, HPMC, TEA, MCC, and water. CM was incorporated into the gel after 24 hours of gel preparation using rapid mixing till homogeneous mixture was produced.

Floating ability

The floating ability of CM gel was evaluated according to the dissolution method described by United States Pharmacopoeia (2018), using apparatus II (paddle): 500 mg of CM gel were added in 400 mL of acidic fluid (HCl 0.1 N, pH= 1.2) at approximately T= 37 °C at a bath of water with periodical stirring at 50 rpm. The lag time and the total floating time were visually analyzed.

Drug release

The dissolution studies were performed using a Dissolution Station (Pharmatest- Germany) based on United States Pharmacopoeia (2018), using apparatus II. The acceptor fluid was maintained at 37 ± 0.5 °C with the rotation speed set at 50 rpm. The release medium was 400 mL of acidic fluid (pH 1.2) for twenty hours. Test was performed in triplicate.

At appropriate time intervals (1, 2, 6, 10, 12, 16, and 20 hours), 10 mL of the samples were withdrawn and filtered. The dissolution medium was replaced with the same volume maintaining the sink conditions.

The filtrate was analyzed by UV spectrophotometer (Hellma- Germany) at 210 nm. The concentrations were calculated using calibration profiles based on absorbance versus concentration curves previously designed and standardized. Formulations were optimized according to USP 41 requirements which indicated the retarding property in acidic the medium after 2, 6, 10, and 16 hours, considering minimal polymer quantity, and well floating properties.

RESULTS AND DISCUSSION

For the results of Clarithromycin gels, only very few samples of the prepared gels floated when added in contact with the acidic fluid.

Nearly one minute was enough for those gels to float and that was for most of the accepted formulations.

The optimal formula contained: CM, HPMC, and Carbopol floated after 0.9 minute, and remained floating till 20 hours nearly (Figure 2).

After one hour, the CM released ratio in the acidic fluid was less than 10%, and that explain how the gel retard the drug release. After 20 hours the ratio of drug release was nearly complete (98.57%).

The results of dissolution studies of the floating CM hydrogel in the acidic medium are compatible with the USP requirements for CM extended release tablets. The results are presented in Figure 3.

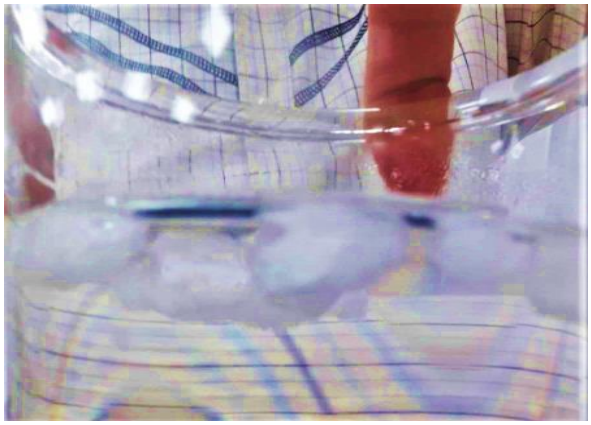

Figure 2: Floating MT hydrogel.

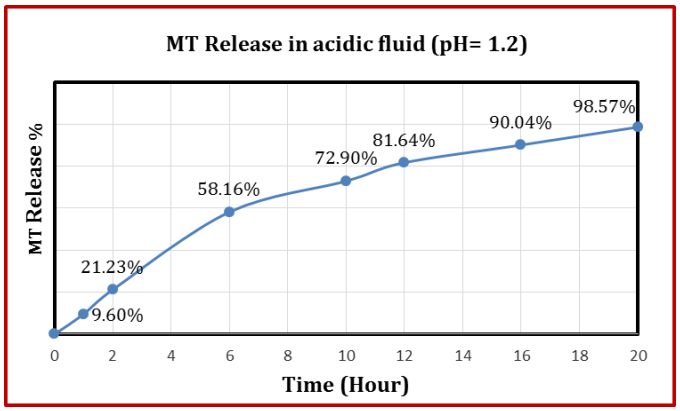

Figure 3: Clarithromycin release profile in acidic fluid.

CONCLUSION

Floating Hydrogels of Clarithromycin using different polymers were successfully obtained for the purpose of gastric retention release.

The results of the chosen formula showed extended release of CM Gel which had floated for 20 hours, and released about 98% from its content within 20 hours.

We need profound studies and further investigations in vitro and in vivo to ascertain the results. The prepared hydrogel can be applied in vivo as an oral dosage form filled in soft or hard capsules for more studies.

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