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FORMULATION AND EVALUATION OF VERAPAMIL HYDROCHLORIDE FLOATING BEADS

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Abstract:
The oral delivery of drugs with a narrow absorption window in the gastrointestinal tract (GIT) is often limited by poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at the site of absorption. There have been many efforts to improve oral drug bioavailability and therapeutic efficacy and patient compliance. A variety of controlled-release oral delivery systems have been developed to meet these needs. Gastroretentive drug delivery systems (GRDDS) such as bioadhesive or mucoadhesive, high-density, expandable and floating, superporous hydrogels and magnetic systems have the potential to achieve retention of the dosage form in the upper gastrointestinal tract (GIT) that can be sufficient to ensure complete solubilization of the drugs in the stomach fluids, followed by subsequent absorption in the stomach or proximal small intestine. In Present work develop a gastroretentive sustained release dosage form of a water-soluble drug, Verapamil hydrochloride, from a completely aqueous environment avoiding the use of any organic solvent, thus releasing the drug for a prolonged duration of time. The effects of factors like concentration of oil, drug: polymer ratio and alginate: pectin ratio on drug entrapment efficiency, floating lag time and morphology and drug release was studied.

Keywords: *Verapamil hydrochloride, Controlled release, Floating beads, Evaluation*

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INTRODUCTION:

Oral drug delivery systems are the most popular dosage forms for drug administration [1, 2]. Many reasons contribute to their dominance, including high patient compliance, easy storage and transportation, cost-effectiveness and those no specialised medical personnel are required to administer. However, poor bioavailability can be an issue for many orally delivered drugs with pH-dependent solubility or stability or a narrow window of absorption. Such properties need to be considered during formulation development since they could cause incomplete drug absorption when the dosage form is transferred towards the lower part of the gastrointestinal tract (GIT) [3-5]. A controlled drug-delivery system with prolonged residence time in the stomach can be of great practical importance for drugs with a narrow absorption window in the upper small intestine. Examples of such drugs include ciprofloxacin [6], sotalol HCl [7], levodopa [8], furosemide [9], ribofavin [10], chlordiazepoxide HCl [11] and cimetidine [12]. Multi-unit floating dosage forms prepared from freeze-dried calcium alginate by dropping sodium alginate solution into calcium chloride aqueous solution were spherical beads of approx. 2.5 mm in diameter can be prepared beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -400C for 24 hours, resulting in the formation of a porous system, which can float for over 12 hours. These floating beads give an enhanced residence time of more than 5.5 hours [13]. Verapamil hydrochloride, a calcium channel blocker is widely used for the treatment of hypertension, angina pectoris, supraventricular tachycardia and myocardial infraction. It is completely absorbed (90%) from the gastrointestinal tract after oral administration but has very low bioavailability of 22±8%. The low bioavailability is owing to the rapid biotransformation in the liver with a biological half-life of 4.0±1.5 hours. The short biological half-life and poor bioavailability of drug favours development of sustained release formulation [14]. Aim of Present work develops a gastroretentive sustained release dosage form (Floating beads) of a water-soluble drug, Verapamil hydrochloride.

MATERIAL AND METHODS:

Material

Gift sample of Verapamil hydrochloride was obtained from Pharmaceutical Company. Sodium alginate, Pectin, Light liquid paraffin, Calcium chloride (anhydrous) was purchased from Central Drug House New Delhi. All other ingredients used were of analytical grade.

Methods

Preparation of Verapamil hydrochloride floating emulsion gel beads with sodium alginate

The technique involved in the preparation of oil entrapped floating beads combination of sodium alginate and pectin in eachdrug polymer ratio was added using emulsion gelation technique. Polymer was dissolved in water with stirring. Oil was added to polymer solution andthe drug was then added. The mixture washomogenized for 15 minutes and was extruded via a needle having diameter of 0.8 mm from a distance of 5cm in to 5% calcium chloride solution with gentle agitation at room temperature. The dropping rate waskept 2ml/min. After washing the beads, they weredried in a tray dryer at temperature of 40^{0}C. The time of drying was optimized by weighing the bead repeatedly, until they obtained a constant weight [15]. Theformulations of the different batches (J1 to J4) are shown in Table 1.

Table 1: Formulation of Verapamil hydrochloride floating emulsion gel beads

Batch No	Polymer conc.(%) w/v	Drug: Polymer	Alginate :Pectin	Oil conc. (%) w/v	Curing time(minutes)
J-1	5	1:0.5	3:2	15	2
J-2	5	1:1	3:2	20	2
J-3	5	1:2	3:2	15	2
J-4	5	1:2	3:2	20	2

Floating time of emulsion gel beads
The gel bead samples (n=10) were placed in a beakerfilled with 50 ml of 0.1 N HCl solution. Temperature was maintained at 37^{0}C. The floating time of bead swas observed for 24 hrs. The preparation was considered to have buoyancy in the test solution only when all the beads floated in it [16].

Determination of drug content
50 mg of beads were weighed and crushed in a pastel mortar and the crushed material was dissolved in 25 ml of water. The solution was kept for 24 hrs. Volume of solution was made up to 50 ml with washings ofmortar. Then it was filtered. The filtrate was assayed by spectrophotometically at 279.5 nm using a UV double beam spectrophotometer (Schimadzu, UV,1700). The drug content and the encapsulation efficiency were determined [17].

Swelling studies
Beads were studied for swelling characteristics. Onlythose batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug loaded beads were taken, weighedand placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37^{0}C. The beads were periodically removed at predetermined intervals and weighed [18]. Then the swelling ratio was calculated as per the following formula:

Swelling ratio =weight of wet beads/weight of dried beads

Drug release studies
The dissolution of Verapamil hydrochloride-loadedcalcium alginate beads was studied using USP Type II dissolution apparatus (Hicon, Grover enterprises Delhi) containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37±0.5^{0}C and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. These samples were analysed forthe drug present in them with help of UV spectrophotometer (UV-1700, Shimadzu). Only those batches were selected for the release study, which have good drug content and drug entrapment efficiency more than 50% [18].

RESULTS AND DISCUSSION:
The shape of beads varies from spherical to disc shape with changing concentration and ratio of polymers. As the total concentration of polymer was reduced from 5% to 4% and then 3% w/v, shape of beads also became spherical to disc like. Table show that size of beads also increases with increasing polymer concentration. In the case of beads prepared with the combination of sodium alginate and pectin, as the part of alginate was reduced, the spherical shape was lost and beads became disc like or of irregular shape. Table 2show mean diameter of beads of each batch were determined by screw- gauge. The mean diameter of varied from 1.069 to 1.95. Shape of beads varies from spherical to disk shaped with changing in concentration and ratio of polymer. As the total concentration of polymer was reduced from 5 to 3% the shape also become spherical to disk shape. Table 2 show that oil concentration is another important parameter effect on size of beads. Increasing the oil concentration, the size of the beads also increased with fixed polymer concentration. For J-2 have all parameter same except oil concentration, the size of beads of J-2 (20% oil) is larger than J-1 (15 % oil). The floating behaviour of beads was also studied. The oil entrapped alginate – pectin beads containing oil floated immediately and remained floating for 24 hours, if a sufficient amount of oil was used Table 2.

Drug content and drug entrapment efficiency were also affected by various parameters. On increasing %concentration of oil the drug content and entrapment efficiency increased, but not at all concentration. When concentration was increased from15 to 20 % the drug content was 32.70 (J-4), and25.58 (J-2) respectively and the entrapment efficiency was77, and 69 % respectively. Another factor affecting the drug content and entrapment efficiency of beads is Drug Polymer ratio. Beads were prepared by using drug: polymer ratio 1:1 and 1:0.5, and 1:2, on increasing the drug ratio, the drug content increased.

Another factor that affected the drug content and drug entrapment efficiency is the Alginate Pectin Ratio. As the proportion of alginate was reduced the drug content started to reduce e.g., Batches J-1, J-2 and J-3 have drug content of 28.00,25.58 and 32.70 % respectively.

In Vitro drug release was also studied. Batches prepared from combination of polymer i.e. with alginate and pectin is different in release pattern. the drugrelease from the batches such as J-1and J-2 have slower than drug release from the batches e.g.J-3 and J-4. The initial release of drug from J-1 and J-2 was 31.30 % and 18.30 % respectively in 15 minutes and 74.90 %&75.50 % in 12 hours respectively but for batch J-3 and J4 was 41.40 % and 34.90 % in 15 minutes respectively and 5.12 and 78.09% in12 hours respectively. Batches prepared with different drug polymer ratio showed different release patterns. If we compare batches J-2, Batch J-2 shows 18.30 % drug release in 15 minutes and 75.50 % in 12 hrs. In this batch the drug polymer are in the ratio of 1:1. Thus it can be concluded that Whenthedrugpolymerratiois1:0.5 as in case of batch J-1, The thin layer of polymer around large amount of drug causes burst release of drug.

But an optimum release was shown by batch J-2 which has a drug polymer ratio of 1:1 table 3.

Table 2: Evaluation of prepared floating beads

Batch Code	Mean Diameter(mm)	Floating Time(hrs)	Drug Content (%)	Drug Entrapment Efficiency (%)
J-1	1.70	>24	28.00	62
J-2	1.75	>24	25.58	69
J-3	1.90	>24	32.70	71
J-4	1.85	>24	10.05	77

Table 3: Evaluation of prepared floating beads

Formulation	% Release 15 min	% Release 12 hours
J-1	31.30	74.90
J-2	18.30	75.50
J-3	41.40	75.12
J-4	34.90	78.09

CONCLUSION:

In Present work develop a gastroretentive sustained release dosage form of a water-soluble drug, Verapamil hydrochloride, from a completely aqueous environment avoiding the use of any organic solvent, thus releasing the drug for a prolonged duration of time. The effects of factors like concentration of oil, drug: polymer ratio and alginate: pectin ratio on drug entrapment efficiency, floating lag time and morphology and drug release was studied. It can be concluded that when the drug polymer ratio is 1:0.5 as in case of batch J-1, The thin layer of polymer around large amount of drug causes burst release of drug.But an optimum release was shown by batch J-2 which has a drug polymer ratio of 1:1.

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