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Formulation and Evaluation of Floating beads of Verapamil hydrochloride

Azhar Danish Khan*, Meenakshi Bajpai

College of Pharmaceutical Sciences, Raj Kumar Goel Institute of Technology 5th km stone Delhi – Meerut Road Ghaziabad (UP) India- 201003

Corres.author: azhardk@gmail.com

Abstract: To develop a multi-unit 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. Emulsion gelation technique was used to prepare emulsion gel beads using sodium alginate as the polymer. The gel beads containing oil was prepared by gently mixing and homogenizing oil and water phase containing sodium alginate which was then extruded in to calcium chloride solution. 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. The use of sodium alginate and combinations of sodium alginate and pectin were used to study the effect on the sustaining property of the formed beads**.** It was found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug**.** The results show that these beads can entrap even a water soluble drug as Verapamil hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time without using any organic solvent and any time consuming step in the preparation.

Key words; Floating beads, Verapamil hydrochloride, Formulation.

INTRODUCTION

Historically, the oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances. [1] Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents and oral drug delivery is by far the most preferable route of drug delivery because of low cost of therapy and ease of administration leads to high levels of patient compliance as well as the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes, consequently much effort has been put into development of strategies that could improve patient compliance through oral route [2]

The de novo design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired region of the gastrointestinal tract and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minute to 12 hr. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs

are preferentially absorbed in upper part of small intestine. Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally average 2-3 hr through the major absorption zone (stomach or upper part of intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, control of placement of DDS in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption [(3)]. Conventional oral dosage forms such as tablets, capsules etc provide specific drug concentration in systemic circulation without offering any control over drug delivery and also great fluctuations in plasma drug levels, by comparison oral controlled drug delivery systems provide a release profile predominantly controlled by the design of the system itself [(4-5)] .It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time [(6-7)]

These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Thus when a drug possesses a narrow 'absorption window' design of sustained release preparation require both prolongation of gastrointestinal transit time of dosage forms and controlled drug release.

Extended release dosage form with prolonged residence time in stomach is highly desirable for drug [(8)]

- That are locally active in stomach
- That have absorption window in stomach or in upper small intestine.
- That are unstable in intestinal or colonic environment
- Have low solubility at high pH value.

The patient always wants to minimize the frequency of dosing without compromising the therapeutic benefit. Use of sustained release dosage forms can fulfill this requirement. Verapamil hydrochloride is a Calcium Channel blocker. The primary absorption region of this drug is stomach. Its oral bioavailability is 22% and half-life is 4 hours and its absorption takes place in upper part of GIT (mainly small intestine). However, bioavailability of drug has been found to be reduced further due to first pass metabolism. Verapamil hydrochloride is absorbed from stomach and upper part of small intestine

The incorporation of Verapamil in an extended-release oral dosage form would have many advantages such as improving the patient compliance by reducing dosing frequency, since the drug is indicated in chronic diseases. In addition, some reports showed that side effects and therapeutic responses were beneficially modified when sustained release forms were used [(9)]. It was also found that solubility of Verapamil HCl is high in acidic environment. The Pharmacokinetic studies show that floating dosage form is better as compared to conventional dosage form [(10)]. The design of gastroretentive drug delivery systems depends upon physicochemical properties, dose and purpose of controlling the drug release, constraining gastrointestinal factors. Various approaches have been pursued including low density dosage form that remains buoyant above gastric fluid or high density dosage form that is retained at the bottom of the stomach, imparting bioadhession to the stomach mucosa, utilizing ion-exchange resin which adheres to mucosa, expending the dosage form by swelling or unfolding to a large size which limits emptying of dosage form through pyloric sphincter, using modified shape system, or other effervescent systems using a gas generating material like sodium bicarbonate and calcium carbonate or the same with citric acid[(11-14)] . Preparation of floating alginate beads is more suitable because it is a multiparticulate system, utilizes cheap and nontoxic polymers and there is no use of any organic solvent. These beads having a sustained release composition and formulation of ranitidine hydrochloride capable of providing release drug release over 12 hr was formulated using expandable, gelling, swellable, hydrocolloid polymer along with light liquid paraffin. Sodium alginate has been used as thickening and gelling agent. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion. Alginate is a linear co-polymer composed of two monomeric units, D-mannuronic acid and L-guluronic acid. They occur in alginate molecule as regions made up exclusively of one unit or the other referred to M block or G block or as a region in which monomer approximates an alternating sequence. Gels form when a calcium salt is added to a solution of sodium alginate in water. The gel forms by chemical reaction, the calcium displaces the sodium from the alginate, holds the long alginate molecules together and a gel is the result [(15)]. No heat is required and the gels do not melt when heated. The polyguluronate block of alginate is known to be responsible for this gelling feature [(16)]. Pectin was also used in combination

with alginate to study its effect on different parameters. It is mainly complex polysaccharide comprising mainly esterified D- galactouronic acid residues in an alpha (1-4) chain; it is also gelled after coming in contact with calcium ions.

MATERIAL AND METHODS

Material

Gift sample of Verapamil hydrochloride (VPHCL) was obtained from Torrent Research Labs Gujarat, India. Sodium alginate, Pectin-pure (poly D-galarturonic acid methyl ester, methoxy content 6%) light liquid paraffin, Calcium chloride (anhydrous) were purchased from Central Drug House New Delhi. All other ingredients used were of analytical grade.

Preparation of Verapamil hydrochloride floating emulsion gel beads with sodium alginate

The technique involved in the preparation of oil entrapped floating alginate beads was emulsion gelation technique. Polymer was dissolved in water with stirring. Oil was added to polymer solution and the drug was then added. The mixture was homogenized for 15 minutes and was extruded via a needle having diameter of 0.8 mm from a distance of 5 cm in to 5% calcium chloride solution with gentle agitation at room temperature. The dropping rate was kept 2ml/min. After washing the beads, they were dried in a tray dryer at temperature of 40^0C. The time of drying was optimized by weighing the beads repeatedly, until they obtained a constant weight. The formulations of the different batches (A-1 to E-2) are shown in **Table-1.**

Preparation of Verapamil hydrochloride floating emulsion gel beads with sodium alginate and pectin blend

The technique involved was similar, only the different combination of sodium alginate and pectin in each drug polymer ratio was added. When only pectin was taken no beads were formed. Homogenizing time, needle diameter, distance of needle from the surface of solution, strength of calcium chloride solution and dropping rate were kept constant.. After washing the beads, they were dried in a tray dryer at temperature of 40^0C. The time of drying was optimized by weighing the beads repeatedly, until they obtained a constant weight. The formulations of these batches (F1 to K2) are shown in **Table2**.

Study of size and morphology of emulsion gel beads

The beads formed were viewed under Scanning Electron Microscope (**Fig1).** The diameter of beads was determined by screw gauge [17] For this purpose, 20 dried beads were randomly selected from each batch and the mean diameter was determined by screw gauge. The least count of screw gauge was 0.005 mm. Colour and shape of dried beads of each batch was noted.

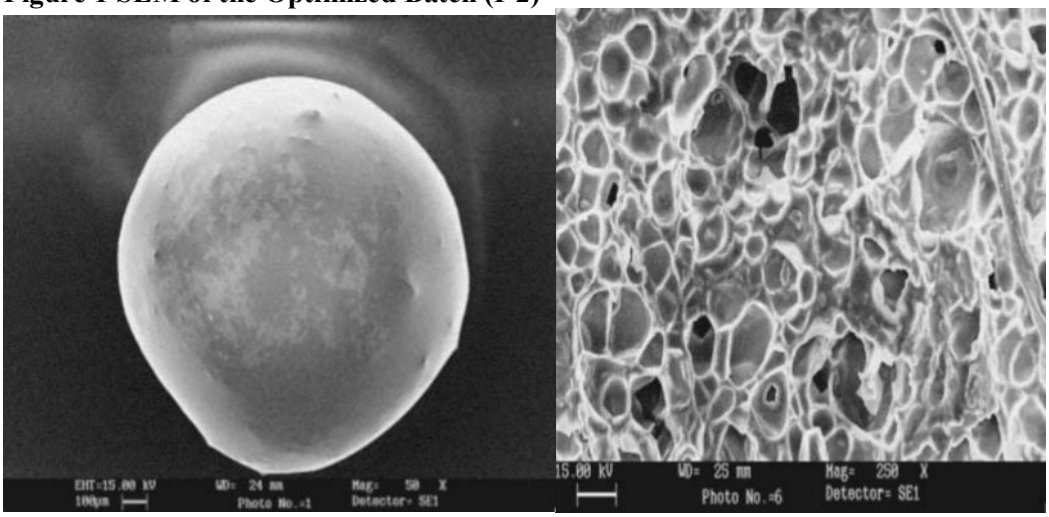
Table 1: Formulation of Verapamil Hydrochloride Floating Emulsion Gel Beads with sodium alginate

Batch No.	Polymer conc. (%) w/v	Drug :Polymer	Oil conc. (%) w /v	Curing time minutes)
A-1	3	1:1	10	2
A-2	3	1:1	15	2
A-3	3	1:1	20	2
B-1	4	1:1	10	2
B-2	4	1:1	15	2
B-3	4	1:1	20	2
C-1	5	1:1	10	2
C-2	5	1:1	15	2
C-3	5	1:1	20	2
D-1	5	1:0.5	15	2
D-2	5	1:0.5	20	2
E-1	5	1:2	15	2
E-2	5	1:2	20	2

Table 2: Formulation of Verapamil Hydrochloride Floating Emulsion Gel Beads with Sodium alginate and Pectin

Batch No.	Polymer conc.(%) w/v	Drug: Polymer	Alginate :Pectin	Oil conc. (%) w/v	Curing time (minutes)
F-1	3	1:1	0:1	15	2
F-2	4	1:1	0:1	15	2
F-3	5	1:1	0:1	15	2
G-1	5	1:1	1:1	15	2
G-2	5	1:1	1:1	20	2
H-1	5	1:1	2:3	15	2
H-2	5	1:1	2:3	20	2
I-1	5	1:1	3:2	15	2
I-2	5	1:1	3:2	20	2
J-1	5	1:0.5	3:2	15	2
J-2	5	1:0.5	3:2	20	2
K-1	5	1:2	3:2	15	2
K-2	5	1:2	3:2	20	2

Figure 1 SEM of the Optimized Batch (I-2)



Floating time of emulsion gel beads

The gel bead samples (n=10) were placed in a beaker filled with 50 ml of 0.1 N HCl solution. Temperature was maintained at 37^0C. The floating time of beads was observed for 24 hrs. The preparation was considered to have buoyancy in the test solution only when all the beads floated in it [18]

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 this solution was made up to 50 ml with washings of mortar. 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.

Swelling studies [19]

Beads were studied for swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug-loaded beads were taken, weighed and 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 37^0C. The beads were periodically removed at predetermined intervals and weighed. 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-loaded calcium 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 analyzed for the 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%.

Study of drug release kinetics [20]

Study of release kinetics of Verapamil HCl from beads was done. The optimized batch was selected for drug release kinetics study. Zero order ($Q_t = Q_0 + K_0 t$), first order ($\ln Q_t = \ln Q_0 + K_1 t$) and Higuchi ($Q_t = K_{11} t^{1/2}$) model were fitted to dissolution data of optimized batch i.e. H-1, using linear regression analysis. Zero order kinetics indicates that the concentration is nearly independent of drug release, while first order kinetics indicates time dependent release kinetics. Higuchi equation explains why the drug diffuses at comparatively slower rate at the distance for diffusion increases, which referred to as square root kinetics.

Table 3: Characterization of floating beads of Verapamil HCl of batch A- 1 to E-2

S. No	Batch Code.	Mean Diameter (m.m.) +S.D.	Floating Lag Time	Floating Time (hrs)	Drug Content(%)	Drug Entrappement Efficiency (%)
1	A-1	1.068±0.09	30 sec	>24	6.86	25.2
2	A-2	1.09 ± 0.075	20-30sec	>24	8.5	26.8
3	A-3	1.14 ± 0.03	0	>24	9.68	27.32
4	B-1	1.15 ± 0.071	1-2 min	>24	11.4	32.12
5	B-2	1.12 ±. 0.02	1-2min	>24	12.1	34.5
6	B-3	1.51 ± 0.045	0	>24	12.2	35.6
7	C-1	1.11 ± 0.021	2 min	>24	13.51	48.2
8	C-2	1.29 ±.0.073	30 sec	>24	14.68	58.1
9	C-3	1.40 ± 0.048	0	>24	19.3	59.05
10	D-1	1.12 ±0.047	3-4 min	>24	30.7	52.1
11	D-2	1.35 ± 0.07	2 min	>24	34.68	62.08
12	E-1	1.36 ± 0.011	0	>24	9.44	61.7
13	E-2	1.41 ± 0.052	30 sec.	>24	10.52	67.88

Table 4: Characterization of floating beads of Verapamil HCl of batch G- 1 to K-2

S.No	Batch Code	Mean Diameter (mm) + S.D.	Floating Lag Time	Floating Time(hrs)	Drug Content (%)	Drug Entrappement Efficiency (%)
1	G-1	1.51 ±0.069	0	>24	18.65	28.5
2	G-2	1.56 ± 0.04	10-20 sec	>24	23.77	33.2
3	H-1	1.77 ± 0.026	10 sec	>24	11	30.53
4	H-2	1.84 ± 0.1	0	>24	11.93	47.32
5	I-1	1.66± .0.067	0	>24	23.5	50.25
6	I-2	1.73± 0.088	0	>24	24.52	68
7	J-1	1.69 ± 0.059	2- 3 min	>24	27	63
8	J-2	1.95 ± 0.026	1 min	>24	32.6	70.8
9	K-1	1.81± .0.014	30sec.	>24	9.52	73.8
10	K-2	1.86 ± 0.1.5	0	>24	9.92	76

RESULTS AND DISCUSSION

Size and Shape 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 3 and 4 show that size of beads also increases with increasing polymer concentration. Beads size of C-2 (5% polymer) is larger than A-2 (3% polymer). 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. The colour of pectin beads prepared in similar way was somewhat darker than that of sodium alginate beads. **Table 3 and 4** show mean diameter of beads of each batches were determined by screw- gauge. The mean diameter of varied form 1.069 to 1.95.The maximum standard deviation 0.011and minimum standard deviation 0.15. Shape of beads varies form 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.As the concentration of pectin increases the shape because more irregular (batches H-1 and H-2).Table 3 and 4 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. Both I-1 and I-2 have all parameter same except oil concentration, the size of beads of I-2 (20% oil) is larger than I-1 (10% oil)

Floating Behaviour The floating behavior 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, but they have different floating lag time (**Table 3 &4**). The different lag time observed due to different oil concentration, polymer concentration, and drug content of the beads. There is decrease in the floating lag time by increasing in oil concentration. Batches J-1 & J-2, have all parameter constants except oil concentration and have different floating lag time. Batch J-2 (20 % oil) has lag time of 15 minutes. Batch J-1 (15 % oil) has lag time of 2-3 minutes.

Drug content and drug entrappement efficiency Drug content and drug entrappement efficiency were also affected by various parameters. On increasing % concentration of oil the drug content and entrapment efficiency increased, but not at all concentration. On using 10%, 15%, and 20% the drug content and entrapment efficiency increased up to 20%. Oil concentration of G-1, H-1 and I-1 is 15 %, and drug content were 18.65, 11, 23.5, (Table 4), and entrapment efficiency was 28.5, 30.53, and 50.25 respectively. When concentration was increased from 15 to 20 % the drug content was 23.77, 11.93, and 24.52 respectively and the entrapment efficiency was 33.2, 47.32, and 68 % 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. Batch C-3, D-2 and E-2 have 5% polymer and all parameter constant only different drug: polymer ratio, the drug content was 19.3, 34.68 and 9.44 respectively, but the entrapment efficiency was 59.05 62.08 and 77.88 respectively. (**Table 3).** 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 G-1, H-1 and I-1 have drug content of 18.65, 11 and 23.5 % respectively

In Vitro drug release: 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 initial release of drug from alginate and pectin entirely different from batches prepared from single polymer (alginate only), the drug release from the batches such as J-2 and I-2 have more slower than drug release from the batches prepared with alginate only e.g. . D-2 and C-2 .The initial release of drug from J-2 and I-2 (**Fig 2a**) was 33.3% and 19.2% respectively in 15 minutes and 75.08, & 75.4 in 12 hours respectively but for batch D-2 and C-2, was 40.42 and 35.7%, in 15 minutes respectively and 75.12 and 78.09 % in 12 hours respectively (**Fig 2b**) . Batches prepared with different drug polymer ratio showed different release patterns. If we compare batches I-2, J-2, and K-2, we will find that these batches have all in common except drug polymer ratio. Batch I-2 shows 19.92 % drug release in 15 minutes and 75.04% in 12 hrs. In this batch the drug polymer are in the ratio of 1:1. But if we take Batch J-2 and K-2 (D:P 1 :0.5 and 1:2) , the initial release was found to be 33.3 % and 9.98 % respectively and the release after 12 hrs was found to be 75.08 % and 67.69 % respectively . Thus it can be concluded that when the drug polymer ratio is 1:0.5 as in case of batch J-2, the thin layer of polymer around large amount of drug causes burst release of drug. But in case of batch K-2 the polymer is double the amount of drug so it holds the drug more firmly and shows a sustained release. But an optimum release was shown by batch I-2 which has a drug polymer ratio of 1:1.

Figure 2 Comparative release profile of different batches

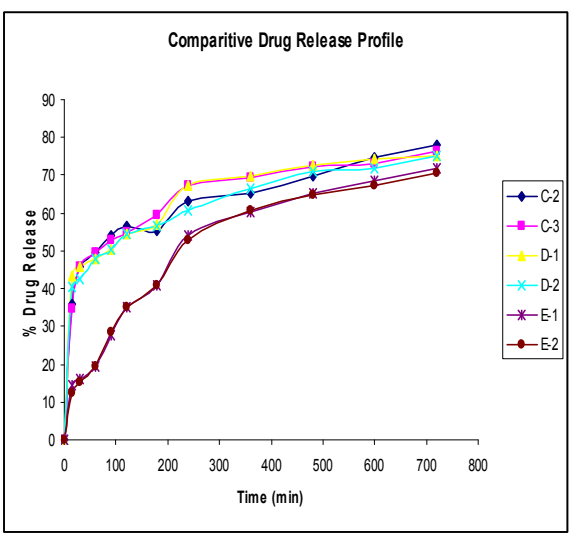


Fig2a

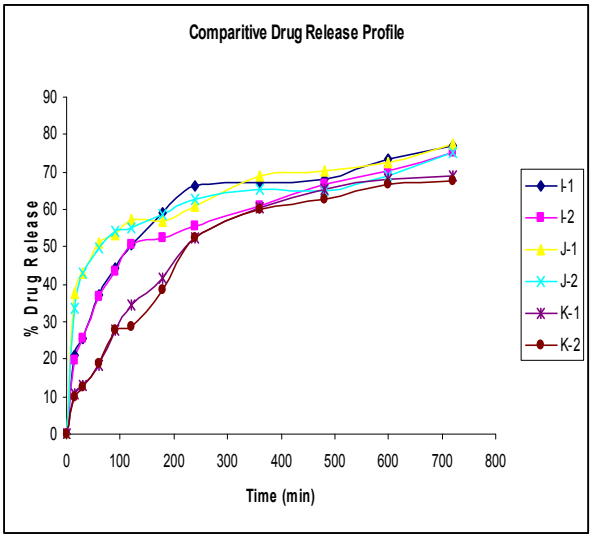


Fig 2b

Figure3 Kinetic Study off the optimized batch (I-2)

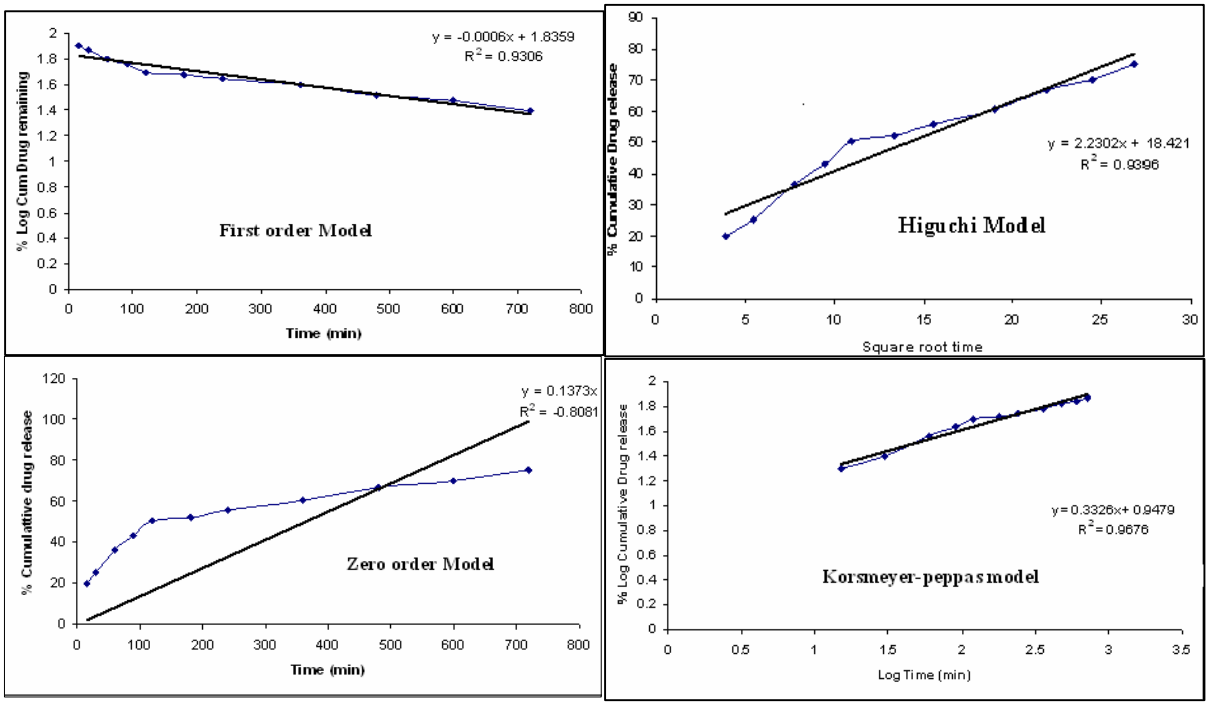
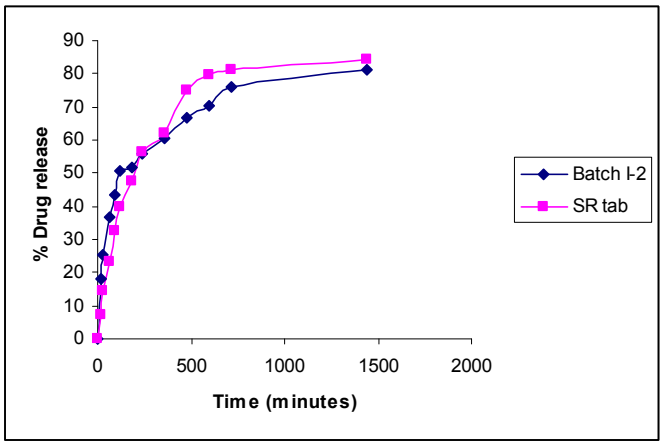


Figure 4 Comparative release profile of Marketed formulation) Calaptin SR tab and the optimized batch (I-2)



Comparison of the Optimized batch I-2 and marketed formulation (fig 4)

To compare the release profile of the optimized batch and the marketed formulation (Calaptin SR tablet, Nicholas Piramal) f2 similarity test was applied .The value of f2 was found to be 49.68.This shows that the products are approaching to similarity (50). Because the release mechanism of drug from the beads and tablet is totally different.

$$f_2 = 50 \cdot \log\{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \cdot 100\}$$

where R is the release profile of the marketed formulation and T is the release profile of the optimized batch (I-2)

After studying all the evaluation parameters it is found that as the polymer was decreased the shape of beads changed from spherical to disc like. When combination of polymers was used then as concentration of alginate was reduced spherical shape of the beads changed to disc like. It can be concluded that alginate is more responsible for spherical shape of the beads.

When floating time was studied it was found that increasing the oil concentration decreases the floating lag time due to less density of mineral oil used. As far as drug content and entrapment efficiency is concerned, increasing the concentration of polymer increases drug content and entrapment efficiency. It may be due to more firm structure of beads due to increased concentration of the polymer. Oil concentration also effects drug content and entrapment efficiency. As oil concentration was increased drug content and entrapment efficiency increased .It may be concluded that higher amount of oil forms an additional barrier and prevents diffusion of the water soluble drug.

After studying various parameters affecting drug content and drug entrapment efficiency, it can be explained increasing the oil concentration increases the drug content due to barrier action of oil which prevented more drug against diffusion. The other factor which affected the drug content is drug: polymer ratio. When the amount of drug is greater, lesser amount of drug diffuses in surrounding aqueous medium. When the amount of polymer was doubled (Batch K-2) the total drug available is entrapped thus increasing the entrappement efficiency.

In vitro drug release was also studied. Beads prepared with alginate alone showed a burst release. When beads prepared with a combination of sodium alginate and pectin were evaluated, they were found to show more sustained release. After comparing this release pattern it is observed that the beads prepared with alginate showed burst release and less sustained effect. This states that for sustained effect a combination of alginate and pectin is required. Thus we can conclude that sustaining effect obtained only with combination of alginate and pectin not alginate only. Thus it can be concluded that only an optimized combination of alginate and pectin can give good sustained effect for Verapamil Hydrochloride. The best sustained effect was given by alginate and pectin in a ratio of 3:2. Drug polymer ratio also plays an important role in drug release. A ratio of 1:0.5 and 1:2 showed a burst and more sustained effect respectively. But an optimum sustained effect was given by a drug polymer ratio of 1:1.After studying all the parameters Batch I-2 was found suitable for delivery of Verapamil Hydrochloride as floating beads.

As shown in **fig 3** plot drawn according to various kinetics models indicate that best linearity was found

in Korsmeyer-peppas (R^2 = 0.9676), hence the formulation follows Korsmeyer-peppas model . It may be concluded that the release kinetics of the drug from the beads was through aqueous pores formed on the aqueous layer. Thus the floating emulsion gel beads of Verapamil hydrochloride prepared with sodium alginate and pectin appears to be a promising vehicle for delivering Verapamil Hydrochloride. These beads can entrap even a water-soluble drug as Verapamil Hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time. Thus without using any organic solvent and any time consuming step in the preparation of these floating beads it is possible to develop an effective, cheap and nontoxic floating delivery system for Verapamil hydrochloride.

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