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Research article

A developed composite hard-gelatin capsules: delayed-release enteric properties

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ABSTRACT

Present study focused on improvement of the formulation of conventional hard gelatin capsules using gastric acid-resistant polymers. We have utilized the same approach of making conventional drug capsules to develop novel capsules with delayed release properties. For this purpose, delayed-release capsules were produced by improving the formulation of hard gelatin capsules. In addition, the effect of adding intestinal polymers such as Hydroxy propyl methyl cellulose phthalate, Glucomannan, and Polyvinyl alcohol to hard gelatin capsules were investigated. The capsules' release rate was determined. The degradation tests in an acidic environment were performed and the results were recorded. In fact, the delayed-release hard gelatin capsules pass through the stomach with small amount of the drug release; but their shell remains intact and dissolves as it enters the intestine environment.

This article shows that enteric polymers with out interactions, only by changing the formulations will have delayed release properties. this makes sensitive drugs pass through stomach environment and have higher absorption.

1. Introduction

In recent years, some of the world's gelatin capsule manufacturers have changed the application of gelatin hard capsules to intestinal capsules by eliminating the coating process and changing the shell production formulation. The gelatin capsules are sensitive to the stomach's acidic environment. The internal contents of drug at acidic pH are released in such environmental conditions. Sometimes, due to the function or effectiveness of some drugs, including supplements, probiotics, or some antibiotics that have failed in the stomach's acidic and internal conditions; in some diseases, such as intestinal diseases, need to be released in desired target. The drug release should be controlled in a targeted and gradual manner. Sometimes it is even necessary to take the drug in a specific environment of the body, or sometimes it is necessary to release the drug at a constant concentration in the digestive system [1, 2].

Utilization of pharmaceutical capsules by modifying their formulation or applying further coating can be considered as one of the suitable solutions. In delayed-release capsules with a shell that is resistant to the digestive system, the drug release is generally controlled by pH and gradual releasing time. This aim is accomplished by using intestinal polymers; while the polymers are resistant to stomach acid. These capsules are inactive when exposed to stomach acid and remain floating in the stomach's digestive fluid [3].

The drug -releasing process gradually begins from the stomach until it reaches the end of the intestine, approximately equal to 20 min and a pH of 1.2. Finally, the capsule's ingredients are completely released at the end of the intestine, and the capsule is completely opened and dissolved. This type of drug delivery system is called the intestinal drug delivery system, categorized as one of the novel drug delivery systems with special therapeutic purposes. Hard gelatin capsules are one of the drug delivery approaches in this system in which polymers with the ability to resist stomach pH are usually used to develop delayed-release properties. These polymers include a variety of natural, semi-natural, and synthetic polymers. Typically, coating the tablets or capsules with polymers causes resistance to stomach pH and lets the capsules passage through the acidic environment. These types of tablets/capsules are called enteric medications [4].

One of the latest methods for coating gelatin capsules is altering the original formulation. In fact, in this method, by adding a polymer resistant to stomach acid to the base formulation and modifying the additive

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ratios, enteric characteristics emerge in the capsules. Accordingly, by eliminating the coating step, the production time, and production costs will be reduced. The enteric method is one of the delayed-release systems aiming. In the current research, we improved the formulation of hard gelatin capsules by compositing with enteric polymers to make acid-resistant pharmaceutical capsules. Consequently, due to the release of the active ingredient from the stomach to the small intestine, such modification led to the fabrication of delayed-release capsules. This study employed hydroxypropyl methylcellulose phthalate (HPMCP) polymer as enteric and stomach acid-resistant polymer [5].

2. Materials and methods

2.1. Chemicals and precursors

All chemicals used in this work were in analytical grade and used in an as-received form with no further purification and process. Gelatin: ($C_{102}H_{151}O_{39}N_{31}$, CAS No.: 9000-70-8) was supplied from Rousselot, used as a base material to prepare capsules. Hydroxypropyl methylcellulose phthalate (HPMCP) (C_8–H_6–O_4.x-C_3-H_8-O_2.x–CH_4–O.x-Unspecified, CAS No.: 9050-31-1) is used as a compositing polymer. HPMCP was chosen according to its properties in conditions such as stomach and small intestine pH to cause delayed-release in the drug while maintaining enteric characteristics of the capsules. Distilled water: is used as a solvent for diluting solutions. Ammonia: (NH_3, CAS No.: 7664-41-7) is used as a solvent for HPMCP. According to the conducted studies ammonia's properties, and international standards, ammonia is a low-risk material and suitable for medicinal applications. Polyvinyl alcohol: (PVA) (CH_2CHOH, CAS No.: 9002-89-5) is used to achieve delayed-release [6]. Glucomannan: $(C_{35}H_{49}O_{29})_n$, CAS No.: 11078-31-2) is used to achieve delayed-release [7]. Polyethylene glycol 600: (PEG) ($H(OCH_2CH_2)_n$ OH, CAS No.: 25322-68-3) is used as a plasticizer and to achieve delayed-release [3]. Further additives, including sodium lauryl sulfate (SLS) ($NaC_{12}H_{25}SO_4$, CAS No.: 151-21-3), methylparaben, ($C_8H_8O_3$, CAS No.: 99-76-3), propylparaben, ($C_{10}H_{12}O_3$, CAS No.: 94-13-3), color, or acetic acid, (CH_3COOH, CAS No.: 64-19-7), which are considered additives in the encapsulation process, can be added to the base combination. Also, 4′-Hydroxyacetanilide (Acetaminophen) ($CH_3CONHC_6H_4OH$, CAS No.: 103-90-2) was used for the drug release evaluations.

2.2. Polymer composite preparation

HPMCP is insoluble in deionized (DI) water and can only be solved in organic solvents. Different types of solvents are water, acetone, ethanol, and ammonia. According to ammonia's characteristics and its lower health risk for humans, compared to the other solvents, it was chosen as the solvent. First, we diluted the solvent. The concentration of ammonia solution was 25%, which is the proper vol.% according to HPMCP solubility. By breaking down the polymer to its monomers, i.e., cellulose units and carboxylic acid-containing esters, and their ionization in the aquatic solution, ammonia solvent helps figure resistance against acidic environments, which prevents capsules damage in the stomach [8]. Since, the supplied ammonia solution was highly concentrated, different vol.% of solvent were prepared by dilution of the original solution with DI water. Then, different wt.% of HPMCP were solved into different diluted ammonia solution achieve the optimal solution. The procedure for preparing a 10% ammonia solution is followed according to the method mentioned in USP37 [9]. To prepare a 10 % ammonia solution, 35 mL of 25 vol.% ammonia solution is mixed with 65 mL of DI water to reach 100 mL final solution. In this study, a 10 % ammonia solution was also prepared and used as a solvent by the same method.

HPMCP was carefully weighed, dissolved in ammonia, diluted with DI water, and then stirred at 300–500 rpm at 65–75 °C for 20 min. This is called solution # 1. Then, glucomannan or PVA was added to solution # 1, and mixing continued. After about 5 min, a PEG-DI water mixture was added to solution # 1, and mixing continued until the solution was entirely homogeneous and all its particles were dissolved. When solution # 1 was entirely homogeneous, gelatin was added and it was placed in a water bath at 55 °C for 30–35 min until gelatin particles were completely dissolved. The product is named solution # 2. Later, the solution was further mixed for 3 min to make it uniform. Then it was placed in a water bath at 50–55 °C for removing bobbles. Finally, solution viscosity was measured, and the solution was kept in the exterior environment for 12 h to remove the remained extra ammonia from the solution. Dipping taken at 38–40 °C, and they were dried at 24 °C and 38–40 % humidity. By preparing different formulations, the optimal ratio of gelatin and HPMCP was obtained Subsequently, the release test was performed to indicate if it is an enteric capsule and having delayed-release Also, we studied the effect of plasticizer agents by using PEG. Accordingly, the amount of DI water vol.% has increased due to the addition of polyvinyl alcohol, PEG-Glucomannan. and Glucomannan. To obtain the PVA-Glucomannan ratio, different amounts of PVA and glucomannan were studied, which are tabulated in Table 1.

Table 1 list the dissolution results of the two final formulations, in which the proportions are optimally performed, and these results are performed in the laboratory. Experimental results indicate that DR8 and DR9 formulations better developed enteric properties and acid resistance, as well as delayed and delayed-release, which are summarized in Table 2.

2.3. Capsule fabrication

For capsule fabrication, we used the dip-coating method. Accordingly, metal pins are deliberately dipped, pulled out from the composite

Table 1. Improved formulations for fabricated capsules.

Substance/ formulation	Gelatin [g]	HPMCP [g]	NH_3 10% [mL]	PEG [g]	Glucomannan	Glycerol [g]	H_2O [mL]	PVA [g]	Capsulation form	Enteric property
DR1*	10	10	10	-	-	2	68	-	✓	×
DR2	10	15	10	-	-	2	53	-	Pouring	×
DR3	15	15	10	-	-	2	58	-	Pouring	×
DR4	20	15	10	-	-	2	58	-	Pouring	×
DR5	20	17	10	-	-	2	51	-	Pouring	×
DR6	20	18	10	-	-	2	51	-	Pouring	✓
DR7	22	18	10	-	-	2	48	-	Pouring	✓
DR8	24	18	10	5	0.1	-	84	-	✓	✓
DR9	24	18	10	5	-	-	84	0.01	✓	✓

*Delayed-Release.
✓ means This indicates that the test was successful and The capsule has enteric properties and capsule formation.
× means The capsule has not enteric properties.

Table 2. Final formulation tests.

Formulation	Solution pH	Temperature [°C]	Pouring	Stomach environment test	Intestine environment test	Release
DR8	5.5	37	×	Intact	Opens at the end of the small intestine	Release begins almost at the 90th minute continues until the end of the small intestine
DR9	5.5	37	×	Intact	Opens at the end of the small intestine	Release begins almost at the 90th minute continues until the end of the small intestine

× means The slow release solution does not fall on the pin.

solution at a constant rate using manual pin bars, while the solution temperature was adjusted to 38 °C and the temperature of the pins was in the range of room temperature. In the high throughput industrial dip-coating, the pins are lubricated with edible lubricants to ease the capsule removal after drying. Consequently, we also lubricated the pins with food oil to enhance the dried capsules removing from the pins.

Afterward, the capsules were dried at room temperature, about 24 °C, with adjusted humidity of 38–40%. However, to speed up the drying process, the pins were dried under blowing air, facilitating faster capsules drying.

2.4. Physical instruments

Quality control is one of the capsule production phases in gelatin capsule manufacturers. We characterized the quality of capsules by conducting analyses, including physical tests such as humidity, diameter, and size test, ash test, capsule collapse time test, and microbial control tests. In this study, field emission scanning electron microscopy (SEM) was performed using VEGA TESCAN-XMU to obtain cross-section micrographs in secondary electron mode. The viscosity of the composite polymer was measured by capillary-tube viscometer according to ASTM D-445. Hygrometry was performed using a Sartorius hygrometer scale with a moisture test in the range of 3–99% and an accuracy of 0.001 to measure the moisture content of the capsules after drying and compare it with the moisture range of conventional hard gelatin capsules. The dehumidification procedure with a psychrometer device is such that 1.5 g of capsules in each stage are placed in the device and then it's the lid is closed, this procedure takes 15 min. Drug release was performed using Dissolution testing system<711 > according to ASTM E2503, USP32 NF27, is a test to determine the release rate of an active drug substance from its solid form (tablets, capsules, etc.). The MTT was measured by MTT test system that was performed (Epoch from BioTek co from USA). Cell culture (1640RPMI) (Gipco) prepared from Institute Pasteur cell bank of Iran. The dissolution test is performed to ensure that the drugs are properly dispersed in an environment. Dissolution test can be done in three steps. Six capsules are tested and if all capsules are less than the allowed limit plus 5%, they are acceptable. If no results are obtained, the other six are tested. If the average of 12 capsules is greater than or equal to the minimum, and is not less than the permissible limit of at least 15%, it is acceptable, if it does not work again, 12 more will be tested. If the average of 24 capsules is greater than or equal to the allowable limit, these capsules are acceptable, and if more than 2 capsules are less than the tolerance of minus 15%, industrial pharmacists regularly test their formulation for dissolution. This device is similar to the human digestive system and according to it, the release of the active drug substance in the gastrointestinal tract can be examined. The dissolution test machine is designed according to USP pharmaceutical standards [9].

3. Results and discussion

According to Table No. 2, it was found that among the solutions 1–9, the two final formulations 8 and 9 were tested three times and each time with 10 capsules in an acidic environment and the same environment as the small intestine, and their release and enteric properties were similar all 3 times and It has been acceptable. The results are also shown in following section.

Figure 1 shows the appearance of transparent delayed-release capsules (Figure 1a) and colored conventional hard gelatin capsules (Figure 1b). It was found that the capsules are almost similar, not even in appearance, but also in terms of physical properties. This means that conventional devices and methods can provide delayed-release capsules with no further modifications.

3.1. Viscosity test

Viscosity defined as the degree of fluidity of a solution. Gelatin-based solutions have a very low fluidity due to their physical properties. Their viscosity can be reduced by adding water. Developed composite polymer solutions have a lower viscosity than pure gelatin solution. Thus, the viscosity should be adjusted according to the solution compatibility with the dip-coating apparatus by adding water. First, a 30 wt.% solution of dry gelatin was prepared. The viscosity was measured at 50 °C. The measured viscosity of developed solutions after the dissolved bubbles disappeared was about 1600 cp; the high viscosity solution needs to be reduced to about 700-650 cp. The initial viscosity is then adjusted by adding water to the initial solutions to be compatible with the dip-coating device's required viscosity. As indicated in Figure 2, the addition of polymers to the solutions, and water to the solvents, it can be said that the viscosity of developed solutions is more compatible with dip-coating devices, and the viscosity adjustment takes less time. Due to the presence of glucomannan, the viscosity of DR8 has increased compared to DR9.

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3.2. Relative humidity

Moisture means the amount of water vapor in a substance. In the process of producing the release delay solution, the amount of water is used for solubility and dilution of the solution; which is finally calculated as the moisture in the capsules after pinning. To calculate the percentage of moisture in the capsules, a hygrometer is used, which considered humidity of the capsules at a specific temperature

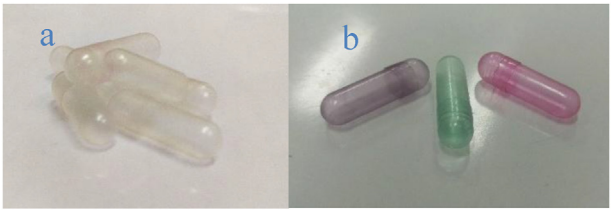

Figure 1. Comparison of the appearance of (a) transparent delayed-release, and (b) colored conventional hard gelatin capsules.

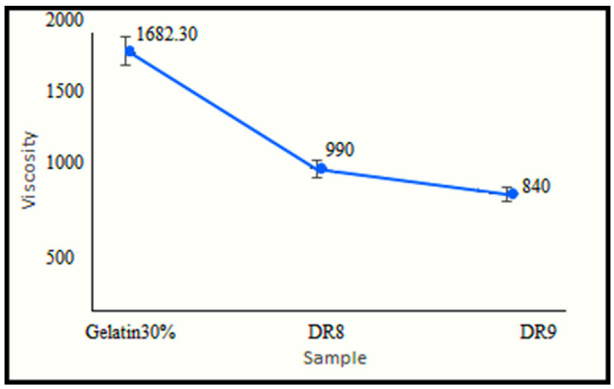

Figure 2. Viscosity comparison of gelatin and developed delayed-release solutions (DR8 and DR9) at 50 °C with 5% Error amount.

and amount. This process was performed by a psychrometer on both developed delayed-release capsules with Glucomannan (DR8) and polyvinyl alcohol (DR9).

Figure 3 demonstrates that the humidity of delayed-release and pure gelatin capsules in each sampling round is almost in the same range. Although, DR9 capsules have more humidity due to the fact that their dehumidification is performed immediately after drying. The relative humidity of gelatin capsules according to USP standard [9] is in the range of 15–16%. In fact, by interpreting the chart, it can be concluded that the relative humidity of delayed-release capsules is not much different from gelatin capsules. Thus, these capsules differ from each other only in performance.

Gelatin, DR8, and DR9, and all three types of them were in the same conditions in terms of duration, measured amount, and environmental conditions in all three rounds of relative humidity measurements. From each of the mentioned solutions, three samples, 1.5 g of capsules were taken in the same conditions to measure their moisture. That is, 3 rounds of sampling were done from gelatin solution, 3 rounds of sampling from the DR8 solution and 3 rounds of sampling from the DR9 solution and 1.5 g of capsule were dehumidified in each round.

This figure has been tested according to the USP standard [9]and the results have been compared and reviewed, the appearance of capsules after dehumidification is displayed in Figure 4. Relative humidity measurements were performed in three turns, which was done to ensure the final result.

3.3. Electron microscopy (SEM)

Cross-section SEM micrographs of pure gelatin, DR8, and DR9 samples are shown in Figures 5a, 5b, and 5c, respectively. The cross-sections were prepared by cutting samples at very low temperatures achieved by a liquid nitrogen environment. Then, samples were coated with a thin gold nanofilm to obtain higher contrast and avoid electron accumulation on the surface [9, 10].

In Figure 5a, by examining the surface of pure gelatin film, it was found that the film's surface was uniform in Figure 5b with no evident bulges. Micrograph of DR8 film in Figure 5b reveals that no interactions occurred between the materials by compositing gelatin with HPMCP and Glucomannan. The appearance of the DR8 surface is quite similar to pure gelatin. This indicates that the film is made of a completely homogeneous and uniform solution, and materials interacted well with each other. The same trend was observed for DR9 film in Figure 5c, in which in compositing HPMCP with gelatin and polyvinyl alcohol no interaction witnessed between materials, and the ingredients are completely homogenized and well combined. In conclusion, by examining cross-section micrographs of gelatin, DR8, and DR9 films, it was found that their surface was not much different from each other, and all three had a smooth surface without any bulges and deformations. Thus, one may conclude that adding polymers to gelatin can only alter their functionality. HPMCP polymer with polyvinyl alcohol and finally it's combination with gelatin are completely compatible with each other, and no interaction has been observed.

3.4. Drug release

Releasing the capsule's ingredients commencing when the capsule's shell degrades. Conventional gelatin hard capsules, enter the stomach in one to 5 min. The capsule's shell begins to degrade due to gelatin's sensitivity to the stomach's acidic environment and release the drug. consequently. However, to maintain a fixed-dose release from the stomach to the small intestine, it is necessary to use natural polymers combined with enteric polymers and gelatin to produce medium sensitivity to the environment. Improving the release stability behavior of capsules reduces the frequency of drug delivery while increases the stability of the dose release in a single dosage. Gastric or intestinal acidity is one of the reasons that delayed-release capsules. should develop. For in-vitro evaluation of release properties, an environment similar to the human stomach and intestines is prepared. Capsules are placed in the artificial environment at 37 °C, and the release of the medicinally active

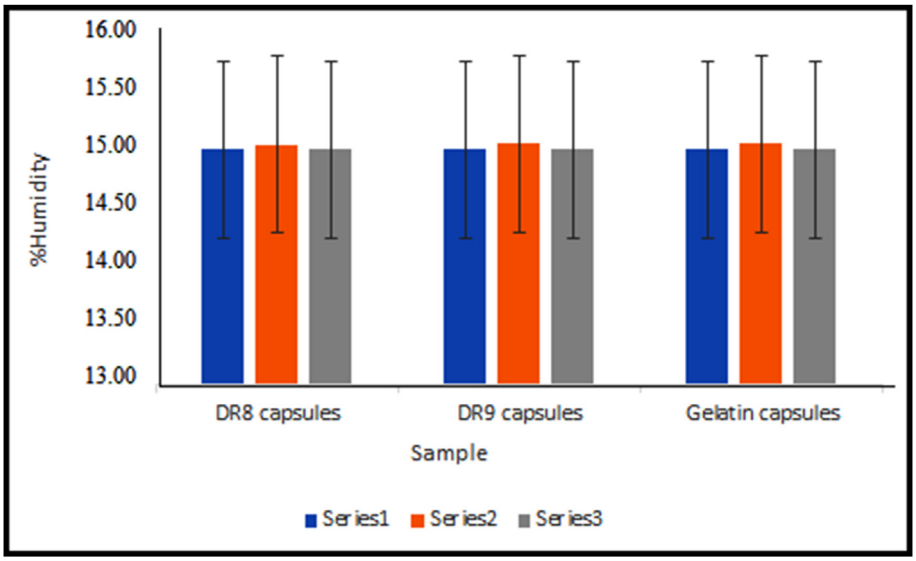

Figure 3. Gelatin and Delayed-release capsules moisture comparison with 5% error amount.

Figure 4. Delayed - release capsules: a: is before and a:is after dehumidification.

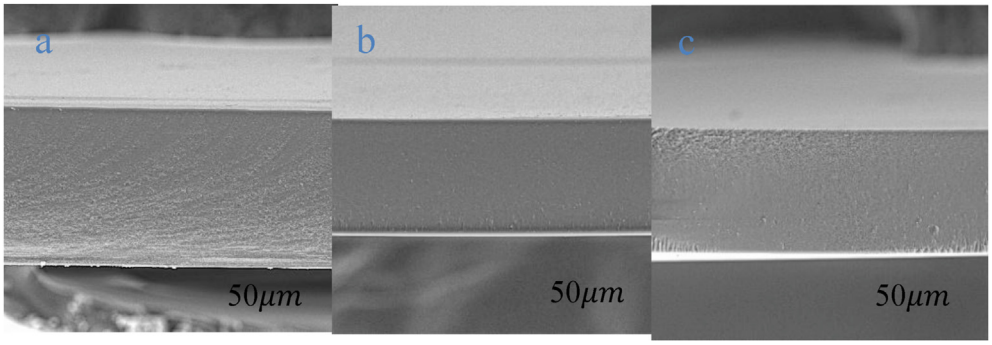

Figure 5. Cross-section SEM micrographs of prepared (a) pure gelatin, (b) DR8, and (c) DR9 films.

ingredient is measured. Capsules filled with acetaminophen powder as an active ingredient and the release rate of capsules were studied and compared with the literature [11]. Acetaminophen is widely using as a pyretic and analgesic [12].

Figure 6a shows the temporal release of acetaminophen in the DR8 capsule. It is evident that the capsule remained completely intact in the first 20 min, passing through the stomach environment. After about 20 min, the active ingredient's release begins with no harm to the capsule's

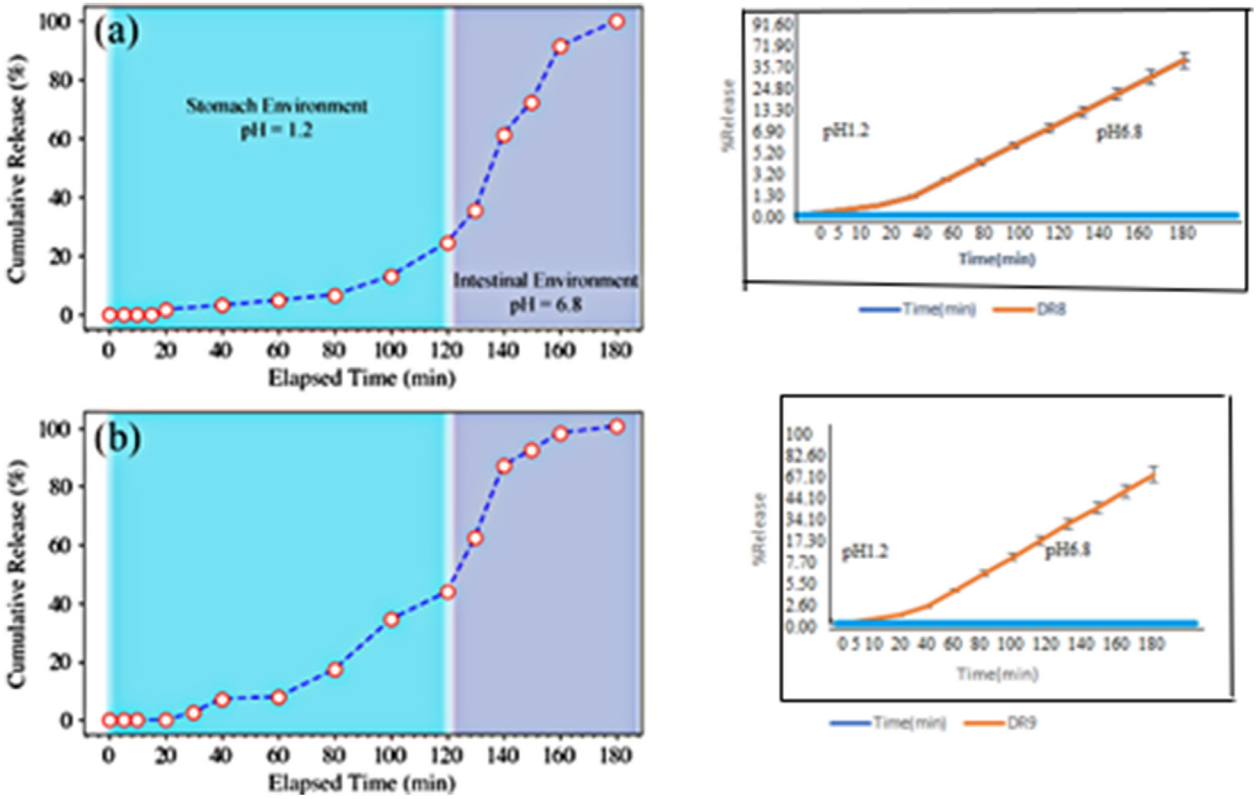

Figure 6. Temporal drug release of (a) DR8 and (b) DR9 capsules.

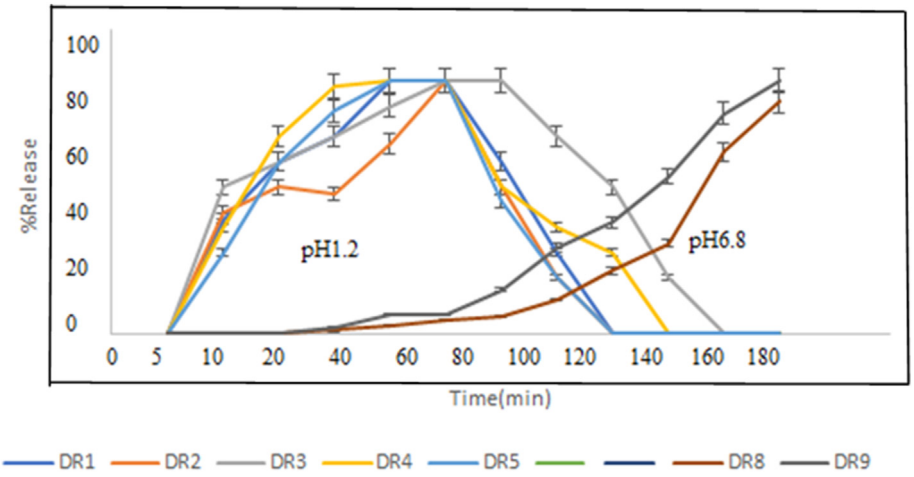

Figure 7. The comparison of capsules with 9 formulations with 5% error amount.

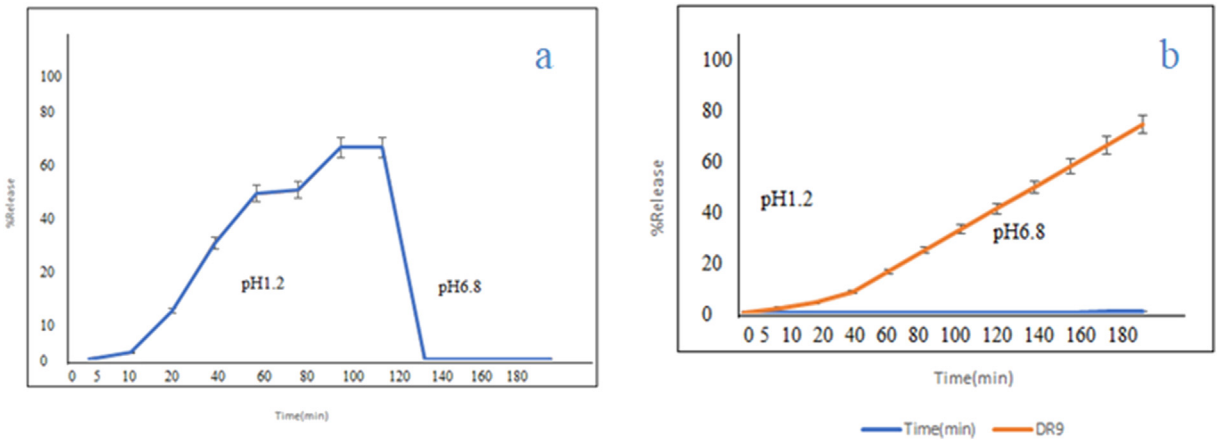

Figure 8. The comparison of Release between Gelatin Capsule and DR capsules.

shell and continues until the end of the stomach. After 120 min, when the capsule reached the beginning of the small intestine, the active ingredient release rate has increased. It should be attributed to the gradual dissolution of the capsule shell in the small intestine. Finally, with the complete dissolution of the capsule's shell, the medicinal ingredient is completely released. Figure 6b shows the drug release from delayed-release was DR9 capsules. The characteristics of DR9 capsules were almost similar to DR8 capsules, and no significant difference in the release was observed. In DR9 capsules, drug release begins after about 30 min and continues while the capsule enters the small intestine, then the capsule's shell begins to dissolve by going into the intestinal, and finally, the drug is completely released. The observed releasing behavior of DR9 in Figure 6b is quasi-parabolic and ascending. However, the slope is higher, and consequently, the rate of medicinal active ingredient release was higher than DR8 at each sampling step. It should be noted that the amount of released drug release at the first moment and overall release rate is slightly higher than DR8 capsules.

The capsules at the end of the stomach, where the shell of the capsule is completely intact. So that the release can be observed by the change of color in the liquid medium. This process was repeated multiple times. In DR8 capsules, release begins 10 min earlier, and the release is more gradual and slower than in DR9. In Figures 6 and 7, the stability of capsules in the stomach's acidic environment and the small intestine's alkaline conditions were examined, and their release properties were evaluated.

Figure 8a, by comparing the release from gelatin capsules, shows that these capsules are completely opened in the stomach environment due to their sensitivity to acid. But Figure 8b shows that in addition to creating an enteric properties, the capsules have the properties of release from the stomach to the intestinal, and then they open completely in the small intestinal, and have achieved the goal of the research.

Figure 9 comparison the release of DR9 capsules (9a) and coated DR capsules (9b). By comparing the graph which has been tested according to the USP standard [9] and the results have been compared and reviewed, it was found that the DR capsules produced by changing the formulation have almost the same release as the coated capsules, So we can say that this research was able to produce capsules with delayed release properties from the stomach to the intestinal by changing the formulation of gelatin capsules and combining enteric polymer HPMCP with it and by removing the coating process in addition to shortening the production process.

3.5. MTT test

MTT test shows cellular metabolic activity. In this test, the color of the MTT solution changes to the color of insoluble Formazan, which only live cells have the ability to do, so the greater the number of live cells in an environment, the greater the color change to formazan and the purple color is observed. at the firs we prepared samples in the form of aqueous solution and then added to the cell culture, after the treatment of live cells, MTT solution is added to it and then penetrates in to the cell wall and formed formazan crystals. In Figure 10, three samples are prepared. In first samples no live cells were observed, so no purple color was observed. But in the second and third samples, purple color change was

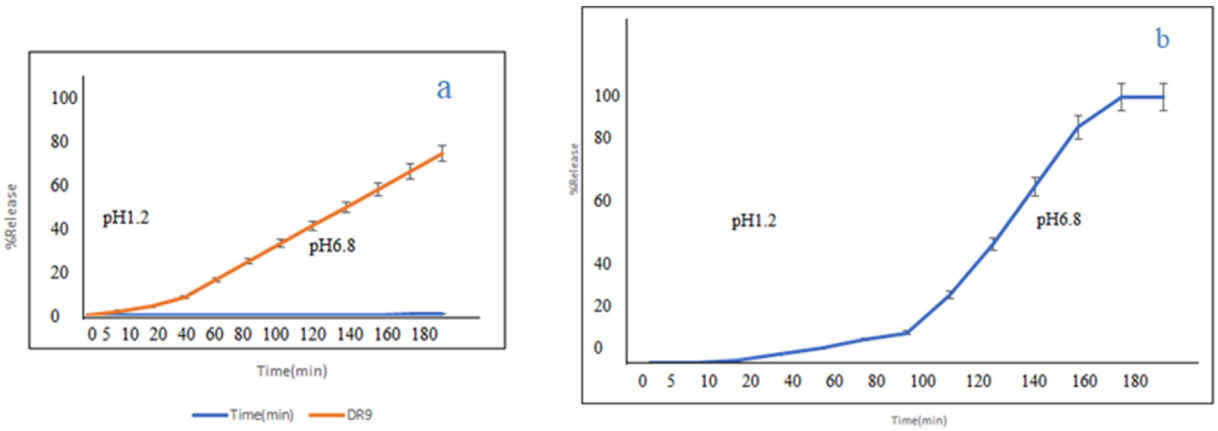

Figure 9. The comparison of Release between DR Capsule coated capsules.

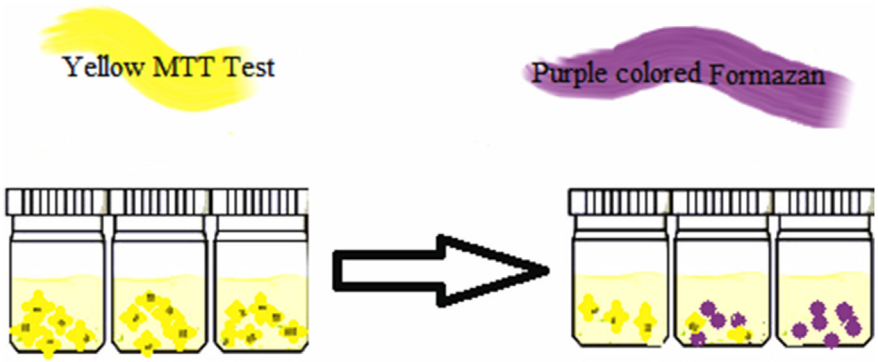

Figure 10. Dehydration of the cell wall of living cells and turning it into purple formazan color.

observed due to the presence of live cells, after dissolve in DMSO solution we can measured in an ELISA reader So conclude that there is no cell toxicity that causes the death of live cells. For calculated the percentage of live cells we use formulation that shown below [11, 13].

100 × average absorbance of control samples / average absorbance of treated samples = percentage of the live cells

By prepare 3 samples of DR8 and DR9 solution with different concentration, it was observed that the solution HPMCP, PVA and glucomannan, increased the cell viability percentage with increased concentration. In Figure 11 it was shown that by performing MTT test, the dispersion of purple color increased, so enteric polymer which used are not toxic and live cells number in solution has also increased. In both of DR8 and DR9 samples, almost similar biocompatibility and non-toxicity have been seen.

According to release graphs, it was determined that when pure gelatin capsules entered the stomach, the capsule's shell gradually degraded due to the sensitivity of gelatin to the stomach's low pH acidic environment. So, the medicinal ingredients were totally released, and then the drug's dosage in the stomach reaches zero. No drug will be released in conventional intestinal capsules, when the capsules enter the stomach, due to polymers' resistivity to the stomach's acid [13]. So, the capsule passes through the stomach sound and intact. Interestingly, by entering our developed delayed-release intestinal capsules into the stomach, after 20 min of immersion in the stomach's acid, the drug's release gradually starts, and the medicinal ingredient is slowly releasing. Except that the capsule shell remains unharmed due to compositing with intestinal polymers. This process continues until the end of the stomach and the release rate gradually increases with respect to time. Further, when the capsule enters to the small intestine, the shell gradually starts to dissolve [14, 15]. Consequently, the release rate increases, and once the capsule shell is completely dissolved, the active ingredient is completely released. This type of capsules can be effective for releasing the drug at a fixed rate and for various treatments such as intestinal treatments. For a more accurate evaluation, capsules were filled. with acetaminophen as a medicinally active ingredient. The test procedure is immersing the capsules in the artificial stomach and intestines environments [16, 17]. The use of these capsules creates a stable release rate from the stomach through the small intestine, and causes better drug performance and a higher release rate in the intestine. Thus, more absorption will be achieved in the intestine that is very useful for many drugs such as Omeprazole or various vitamins and supplements which causes higher efficiency and more effective treatment [18]. According to our studies and evaluation of different

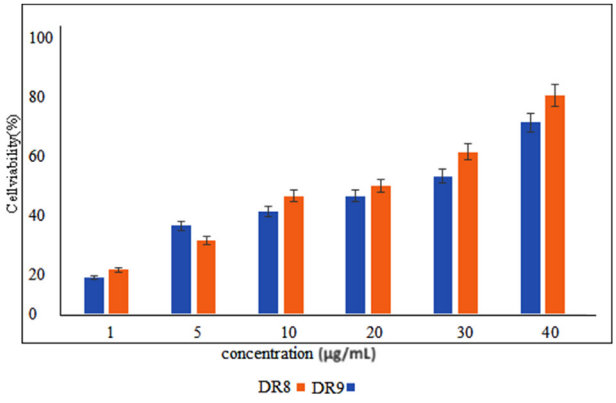

Figure 11. Cell viability percentage with increasing concentration with 5% error amount.

formulations, the best and most optimal ratios shave been achieved to produce delayed-release capsules. Therefore, capsules with controlled and delayed-release properties were achieved, which is an effective form of targeted drug delivery [19, 20].

4. Conclusion

In this study, we tried to enhance gelatin capsules' intestinal properties by improving the chemical formulation of hard gelatin capsules. Developing delayed-release intestinal capsules based on conventional gelatin hard capsules reduces the production time and leads to a lower total price. Developing intestinal capsule was performed by improving the chemical formulation of gelatin-based hard capsules by compositing with Glucomannan or PVA.

These developed solutions were also examined on capsule production machines on an industrial scale, which yielded a very satisfactory result. It means that with a slight modification in production conditions, intestinal capsules with controlled and delayed-release properties can be made using the same industrial machines. These capsules can also be produced with an herbal alternative as the gelling base material instead of gelatin. Also, since HPMCP has brittle properties and its use at higher ratios can reduce the quality of the capsule and cause brittleness, other enteric polymers can be used to create enteric properties in the solution.

According to the evaluated release properties and SEM micrographs and MTT test, it was found that all materials are compatible with each other, and with the body. Therefore, it can be an excellent candidate to be substituted with coated capsules. Hence, it can be said that the purpose of the study, which was to achieve capsules resistant to stomach acid and with delayed-release for specific therapeutic purposes, was achieved.

4.1. Limitations of the study

The limitation of the study is the excessive use of hydroxypropyl methylcellulose phthalate in combination with gelatin, because it will make the capsule shell brittle and its shape improper. Also, the use of polyvinyl alcohol in the composition should be in proportion to the gelatin and HPMCP. The next thing is that other natural polymers can be used instead of HPMCP to create intestinal properties. This improves the shell quality of the intestinal capsules.

4.2. Further research plan

We aim to replace gelatin with Modified Starch and combination with enteric polymers. Also, other natural enteric polymers can be used instead of HPMCP, so that the delayed release capsules has better physical properties.

Inclusion and diversity statement

In this study, the capsules were tasted in the laboratory. Due to the naturalness of the polymers used, the same result is thought to the observed in animal and human tests.

Declarations

Author contribution statement

Mozhgan Mohseni: Performed the experiments; Wrote the paper.
Azin Jahani: Conceived and designed experiments.
Ghasem Njafpour Darzi: Analyzed and interpreted the data.
Ramin Ramezani: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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