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Original Article

Design and Evaluation of Delayed-Release Osmotic Capsule of Acetaminophen

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Abstract

Hard gelatin capsule filled with acetaminophen, osmotic agent (sorbitol), a release promoter (sodium dodecyl sulfate), coated with a semipermeable cellulose acetate membrane containing a hydrophobic plasticizer (castor oil) and sealed with white bees wax plug was designed. When placed in the sink water penetrates the membrane, dissolves the osmotic agent and increases the osmotic pressure inside the capsule. The increased osmotic pressure enhances the water imbibition and consequently increases the hydrostatic pressure inside the capsule and when the latter pressure is high enough it expels out the plug and the drug release commences. With cellulose acetate concentration constant in membrane forming solution, 11% (w/w), the factors affecting the onset of the drug release, i.e. the lag time (t_L), were thickness of semipermeable membrane (0.033-0.112 mm) and plug thickness (2.40-3.40 mm) although the influence of semipermeable membrane thickness was more important than plug thickness in delaying the onset of release. As the statistical analysis revealed, castor oil concentrations in the range of 3-4% (w/w) did not affect the lag time. With the control of the membrane thickness, the onset of release could be adjusted from 2 to 7 h. The formulations with t_L of 3.9 and 5.8 h may have practical benefits in that if such systems are administered simultaneously with conventional forms the 6 and 4 times daily drug dosage frequency would be reduced to 3 and 2 times regimens, respectively. A theoretical justification was provided for the observed nonlinear relationship between the onset and/or t_L of drug release and thickness of the semipermeable membrane. After the lag time, the drug release from the systems conformed to the USP requirements.

Keywords: Acetaminophen; Cellulose acetate; Delayed-release; Onset of release; Osmotic capsule.
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1. Introdution

A delayed release profile, where the drug is released completely after a defined lag time, t_L, has advantage over sustained-release dosage forms for drugs which develop biological tolerance, with an extensive first pass metabolism, targeted to a specific site in the intestinal tract and for the adaptation of therapeutic needs to circadian rhythms of body functions or diseases. Another important benefit of the delayed-release systems which is also in common with the sustained-release dosage forms is reduction of frequency of daily drug dosage [1-7]. Several approaches to delay or create the t_L in drug release exist. Some systems contain a drug reservoir, surrounded by a barrier which either erodes or dissolves [8-10], or ruptures [11-15]. With eroding or dissolving systems, a potential problem is the retardation and, therefore, not immediate drug release after the loss of the barrier function or a premature release, seen in particular with highly water-soluble drugs [16]. Capsular-shaped systems are more independent from the nature of the content, and systems consist of an insoluble capsule body with swellable [17] or erodible plugs [18] have been reported. Another capsular system exploits the osmosis principle to control the t_L and/or drug release onset. Such a system has been the subject of some patents [7, 13] one of which with the active ingredient of methylphenidate has been commercialized and used in attention deficit hyperactivity disorder, ADHD, [1]. The system consists of a hard gelatin capsule coated with a semipermeable membrane (e.g. cellulose acetate) housing an insoluble plug (e.g. lipidic) and an osmotically active agent along with the drug formulation. To the best of our knowledge, the details of formulation as well as theoretical aspects of such a system have not been provided in literature. The objective of the present study was to design and evaluate a capsular system of a model drug, acetaminophen, employing osmosis principle with some different ingredients. The drug has a high frequency of dosage in some fever and pain relief situations up to 6 times daily which justifies its formulation as a delayed release osmotic capsule. The factors affecting the onset of the drug release, i.e. the t_L, including the thickness of plug and semipermeable membrane as well as concentrations of castor oil in coating solution have been investigated statistically.

2. Materials and methods

2.1. Chemicals

Acetaminophen, sorbitol, sodium dodecyl sulfate, cellulose acetate, castor oil, magnesium stearate, acetone and white bees wax were purchased from Merck (Darmstadt, Germany).

2.2. Preparation of coating polymer solution

Cellulose acetate (CA) as a semipermeable

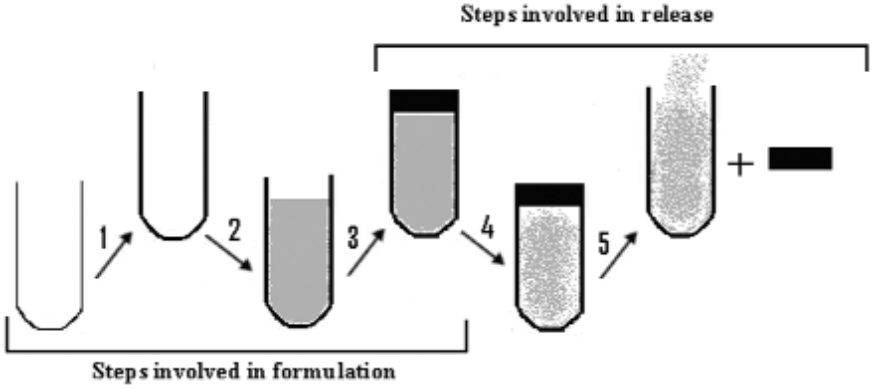

Figure 1. Key steps in formulation and release of acetaminophen osmotic capsular system: (1) semipermeable coating; (2) ingredients filling; (3) placement of plug; (4) simultaneous build up of osmotic and hydrostatic pressures inside the capsule due to water penetration from the sink; and (5) start of drug release after plug expulsion.

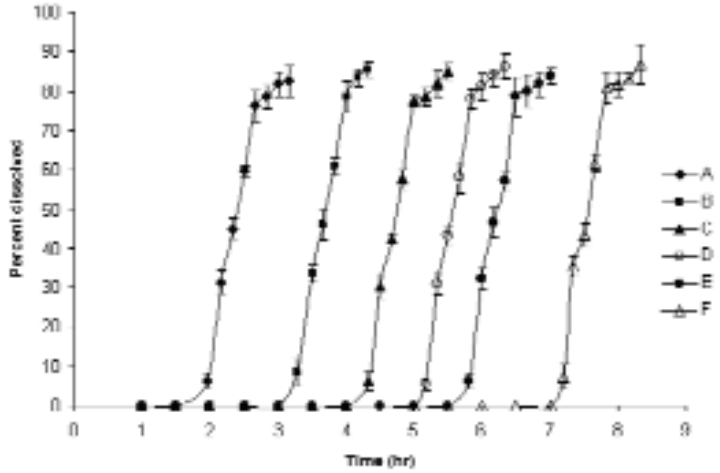

Figure 2. Dissolution curves of delayed-release capsular osmotic systems of acetaminophen for formulations A-F. Each point is mean of 4 tests and error bars represent standard deviations. Details of formulations are shown in Table 1.

membrane forming polymer and castor oil as a plasticizer as well as hydrophobic agent (for controlling water penetration rate to semipermeable membrane) were dissolved in acetone by stirring at the room temperature to obtain the desired concentrations.

2.3. Coating of capsule body

Transparent and colorless size 00 hard gelatin capsules were coated by dip coating method at the room temperature. The coated capsules were then dried at different temperatures ranging from approximately 25 to 50 °C for 15 min. in order to find an optimum temperature for obtaining smooth coat without any shrinkage. Smooth coating was formed when the temperature was 25 °C. Thickness of the semipermeable film applied to the capsule could be varied by altering the number of coats applied. Number of coats was between 2-5 times and each coating process was carried out after drying the previous coat.

2.4. Measurement of coat thickness

Empty capsule body was coated by the dip coating process under the condition used in this study, then the thickness of the dried coat after peeling was measured with a digital micrometer (Mitutoyo, Kawasaki, Japan).

2.5. Filling of the capsule body

The coated capsules were hand filled with acetaminophen powder as an active ingredient (100 mg), sorbitol as an osmotic agent (260 mg), sodium dodecyl sulfate (SDS) as promoter of drug release after plug expulsion (1% w/w) and magnesium stearate as lubricant for improving powder flowability (1% w/w).

2.6. Acetaminophen content

The acetaminophen contents of 5 capsules were chosen randomly from each formulation and determined spectrophotometericly at 243 nm (Shimadzu-mini-1240, Japan) after dissolving and appropriate dilution in water.

2.7. Preparation and placement of plug

In order to form the plugs with 3.40 and 2.20 mm thicknesses, 26 g and 17 g of white bees wax were melted in glass Petri dish with diameter of 10 cm and were cooled at about 32 °C. Then, the Petri dishes were carefully inversed on the open end of the capsule body and the capsule was pushed to the layer of the wax for the formation of plug.

2.8. In vitro release

The release tests of the prepared formulations were performed in a USP apparatus II. The dissolution medium was

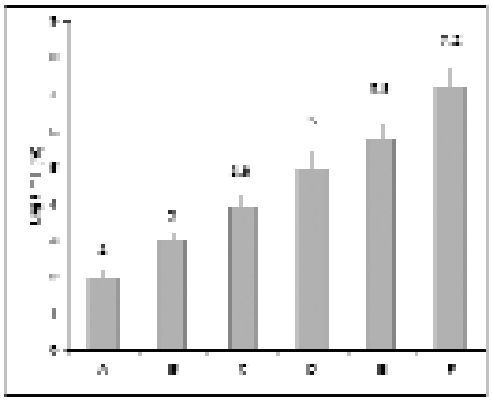

Figure 3. Histograms showing the mean lag times of acetaminophen formulations A-F. Each value is average of 4 experiments and the bars represent standard deviations. All mean lag times are statistically significant with each other (p<0.05). Details of formulations are seen in Table 1.

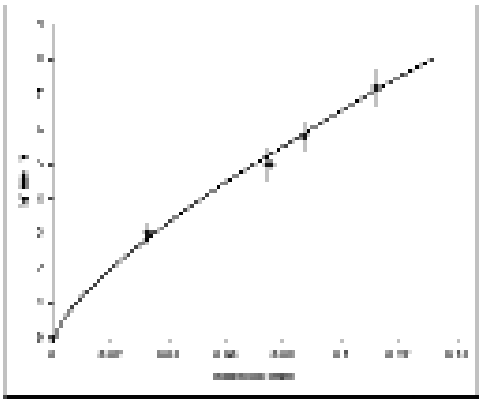

Figure 4. Relationship between mean lag time in drug release and/or onset of drug release with mean thickness of semipermeable membrane. Each value is average of 4 experiments The curve is calculated by equation (7) and the symbols are experimental data. The vertical bars represent standard deviations.

900 ml distilled water. The temperature was 37 °C and stirring rate was 50 rpm. Samples (5 ml) were taken from the dissolution medium every 30 min. before plug expulsion and thereafter 8 samples every 10 min. and replaced by equal volume of the medium. Each dissolution profile was the average of 4 tests. Altogether 24 dissolution tests were performed. Acetaminophen concentration was assayed spectrophotometically as mentioned above. *In vitro* t_L was calculated by extrapolation to the time axis of the initial steep portion of each individual release curve.

3. Results and discussion

3.1. Description of the processes and formulations

The key processes involved in formulation and release of the acetaminophen capsular systems are illustrated in Figure 1. These are coating the capsule with CA, filling the ingredients, placement of the plug, dissolution of the osmotic agent due to water penetration from the sink, simultaneous build up of osmotic and hydrostatic pressures inside the capsule, plug expulsion due to hydraulic pressure and start of drug release. The concentrations of formulation components including CA as well as castor oil in membrane forming solution, number of coatings and thicknesses of plugs and semipermeable membrane are shown in Table 1. The drug contents were between 96.5-102.3% of theoretical values.

3.2. Drug dissolution and lag time

The drug dissolution profiles of different formulations are given in Figure 2. The dissolution from all formulations fulfilled the USP requirements for acetaminophen capsules

Table1. Formulation components, number of coatings and thicknesses of plugs and semipermeable membrane.

Formulations	Number of coatings	Castor oil (%)w/w	Cellulose acetate (%)w/w	Coat thickness (mm) [a]	Plug thickness (mm) [a]
A	2	3	11	0.033(± 0.004)	2.20(± 0.30)
B	2	3	11	0.033(± 0.004)	3.40(±0.42)
C	3	3	11	0.052(± 0.005)	2.20(± 0.32)
D	4	3	11	0.075(± 0.006)	3.40(±0.44)
E	4	4	11	0.087(± 0.008)	3.40(±0.46)
F	5	3	11	0.112(± 0.012)	3.40(±0.44)

[a]Each value is an average of four measurements and fihure inside parenthesis is the standard deviation. Total number of formulations is 24.

in that at least 75% of the dose was released in 45 min. [20] following the plug expulsion. After commencement of the release, the dissolution rates of the drug from different formulations were nearly equal as judged from the times required for 50% dissolution ($t_{50\%}$) which were between 0.57 to 0.60 h. The reason for this equality of the rates is obvious because the ingredients inside the capsules are all the same. The mean values of t_Ls together with the standard deviations are depicted in Figure 3. Depending on the formulations, the mean t_L values varied between 2-7.2 h. The statistical level of significant difference among the mean values was analyzed after performing ANOVA and Tukey multiple range tests using SPSS version 11.5 package. The result of analysis indicated that the t_L of all formulations (A-F) were significantly different from each other ($p<0.05$). The difference between formulations A and B with equal semipermeable membrane thicknesses and the same plasticizer concentration is merely due to difference in their plug thicknesses. Formulation C despite having thinner plug thickness exhibits significantly longer t_L than formulation B indicating the importance of semipermeable membrane thickness (0.052 *vs* 0.033 mm). In formulation D both plug and semipermeable membrane thicknesses are greater than formulation C which results in greater t_L. Formulation E possesses higher hydrophobic plasticizer concentration and thicker semipermeable membrane thickness and thus these factors account for its longer t_L value with respect to formulation D. Although formulation F contains lower plasticizer concentration than formulation E, it shows longer t_L because of thicker semipermeable membrane thickness. Inspection of data for formulations D-F in Table 1 reveals that the influence of the plasticizer in the range of used in this work (3-4% w/w) is negligible in comparison to that of the semipermeable membrane thickness. In these formulations which have equal plug thickness the value of t_L becomes longer as the semipermeable membrane thickness increases.

3.3 Mechanism of drug release

When the capsular osmotic system is placed in the sink, water molecules penetrate the capsule, dissolve the osmotic agent, and solution of the agent is formed inside the capsule. As a result, the chemical potential and/or thermodynamic activity of water molecules in solution of the osmotic agent inside the capsule decreases in comparison with that of pure water molecules outside the capsule which causes an increase in the osmotic pressure of the capsule content. In other words, the chemical potential gradient of water molecules between inside and outside the capsule leads to the influx of more water which in turn enhances the hydrostatic pressure of inside the capsule. When the hydraulic (hydrostatic) pressure is high enough to overcome the gravity and frictional forces of the plug, it causes expulsion of the plug from the capsule and drug starts to release into the sink. It should be mentioned that all the times including the moment of plug expulsion both osmotic and hydrostatic pressures inside the capsule are equal The osmotic pressure produced by saturated solution of sorbitol (940 mg/cm^3) is reported to be 123 atm [19] (1 atm = 101325 Nm^{-2}). Considering the volume of capsule size 00 (1 cm^3) as well as the amount of sorbitol used (260 mg) and ignoring the volumes occupied by the plug, drug and other ingredients inside capsule, the potential osmotic pressure produced by the same concentration of sorbitol in1 cm^3 solution would be roughly (260/940) × 123 = 34 atm [21]. The contribution of acetaminophen to the osmotic pressure is not taken into account due to its very low solubility (14 mg/cm^3) in comparison to sorbitol. Figure 1 illustrates the events involved in the release. The mathematics of the closed osmotic capsular system has not been given in literature. However, some insight can be gained from the

theory of the elementary open osmotic pumps to find a semitheoretical basis for the present closed osmotic system. The factors governing the rate of penetration of water, *dV/dt* expressed as volume/time, to the elementary osmotic pumps in which the rates of water input and exit of drug solution are equal and nearly constant are given in the following general simplified equation [21]:

$$\frac{dV}{dt} = \frac{Ak}{h}\pi \qquad \text{Equation (1)}$$

Where *A* denotes surface area of the semipermeable membrane with the dimensions of (length)^2, π is osmotic pressure (mass/length/time^2) inside the pump which is constant, *k* is diffusion coefficient of water molecules to the membrane (length^2/ time/pressure) and *h* is thickness of the membrane (length). For the reasons mentioned, the drug release kinetic from the pumps is usually zero order. However, in the present closed capsular system, the penetration rates of water into the system as well as the osmotic pressure inside the system are not constant. Hence the integration of equation 1 when the weight of plug remains constant between times 0 and t_L, the delay time in release which is assumed to coincide with the plug expulsion, yields:

$$V_e = \frac{Ak}{h}\int_0^{t_L} \pi.dt \qquad \text{Equation (2)}$$

V_e is volume of the osmotic agent solution at the time of plug expulsion and the integral represents the cumulative osmotic pressure inside the system during the t_L. It is assumed that the integral has a relationship with t_L in the form of equation 3:

$$\int_0^{t_L} \pi.dt = M(\pi_e t_L)^a \qquad \text{Equation (3)}$$

Where π_e is the osmotic pressure inside the system at the time of plug expulsion and *M* and *a* are constants. As mentioned before, π_e is equal to the hydraulic pressure, Hp, inside the capsule at the moment of plug expulsion. Substitution from equation 3 into equation 2, replacing π_e by Hp and subsequent solution for t_L results in equation 4:

$$t_L = \frac{1}{\mathrm{Hp}}\left(\frac{V_e}{APM}\right)^{1/a} \qquad \text{Equation (4)}$$

In which *P* is permeability coefficient of water to the membrane with the dimensions of length/time/pressure and is given by *P*=k/h. The permeability coefficient increases with the porosity, E, of the membrane and decreases with tortuosity, T (extent of bending or twisting) of submicroscopic channels in the wall of membrane that is *P* is proportional to the ratio of E/T. For a given membrane forming polymer, upon multiple coating, the ratio and thus the value of P is inversely related to the membrane thickness by:

$$P=Q/h^m \qquad \text{Equation (5)}$$

Q and m are constants. Substituting P in equation 4 from equation 5 gives:

$$t_L=Bh^b \qquad \text{Equation (6)}$$

in which $B=(1/\mathrm{Hp})(V_e/AQM)^{1/a}$ and b = m/a.

The value of Hp depends on gravity and frictional forces of the plug thus in the formulations with the same plug thicknesses and nature its value is equal. V_e would be the same for these cases. Q and M become constant if the same semipermeable membrane polymer and plug are used in the formulations. Since A is kept constant in the formulations, therefore, B is a constant as well. Under these assumptions t_L would only depend on h^b. The assumptions hold for formulations B and D-F because the nature of the plug and their thicknesses (3.40 mm) are the same. Also the effect of castor oil concentration on t_L is insignificant in the case of formulations E and F. Thus the mean values

of t_L and h of these formulations can be used to demonstrate the validity of our proposed semi theoretical equation 6. In addition to the data of the mentioned formulations, the data of zero semipermeable membrane thickness (h=0) and its corresponding lag time (t_L=0) was also included in the validity test. The assumption of zero lag time for the hard gelatin capsule body without semi-permeable membrane was reasonable because our experience indicated that hard gelatin capsule body disintegrated and dissolved rapidly in less than 0.08 hr. Equation 6 becomes:

$$t_L = 36.00h^{0.74} \quad r^2 = 0.997 \quad n=5$$

Equataion (7)

It should be mentioned that the linear relation between t_L and h for the same data resulted in a smaller r^2 value of 0.984 indicating the superiority of the proposed theory to the pure empirical linear relationship. The theoretical curve of calculated t_L vs. h as well as experimental t_Ls are shown in Figure 4.

4. Conclusion

The delayed release capsular osmotic system of acetaminophen can be designed with suitable bees wax plug and appropriate thickness of CA semi permeable membrane containing castor oil as plastisizer and hydrophobic agent. By adjusting the thickness of the membrane it is possible to control the onset of drug release between 2 and 7 h provided that other variables are kept constant. The formulations with t_L of 3.9 and 5.8 h may have practical benefits in that if such systems are administered simultaneously with conventional forms the 6 and 4 times daily drug dosage frequency would be reduced to 3 and 2 times regimens, respectively. A theoretical basis for drug release from such a system is also given which can be of use to express quantitatively the effect of the membrane thickness on the onset of release.

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