

Design and development and evaluation of candesartan cilexetil liquid filling formulations

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Abstract

Most of the currently available drugs are having poor water solubility and suffer from low oral bioavailability. One of the most promising approaches to deliver such insoluble drugs is by dissolving it in lipids, liquids or semi-solids to formulate new products.^[1] Candesartan meets the requirement of high potency but it is poorly absorbed when administered as tablets. Therefore the prodrug Candesartan cilexetil is developed.^[2] Two piece hard gelatin liquid filling capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations.^[1] Liquid filled formulations were prepared by employing different cosolvents and surfactants. The formulation containing SLS-2%, PVP- 17.5%, PEG-15%, and PG-53% exhibited desire solubility, rheological property and found to be stable in hard gelatin capsules.

Key words: Candesartan cilexetil, poly ethylene glycol, sodium lauryl sulphate, poly vinyl pyrrolidone, liquid fill hard gelatin capsules

INTRODUCTION

Oral route is the easiest and most convenient route of drug administration, being noninvasive and cost-effective, thereby leading worldwide drug delivery market. But major problem encountered in oral formulations (as estimated >50% of oral formulations are found to be poorly aqueous soluble), is low bioavailability, giving rise to further problems like, high inter and intrasubject variability, lack of dose uniformity, and finally leading to therapeutic failure. The challenging task is to increase the bioavailability of drugs.^[3,4]

Capsules are solid dosage forms in which the medication contained within gelatin shells. The medication may be a powder, liquid or a semisolid mass. Capsules are usually intended to be administered orally by swallowing them whole. The capsule provides a tasteless, odor-less delivery system that does not require a secondary coating step so from the patient point of view

many patients find swallowing capsules easier than swallowing tablets.^[5]

Liquid-fill hard gelatin capsule technology is becoming increasingly accepted by the pharmaceutical industry and while it can be hardly expected to replace more conventional dosage forms such as tablets and powder-filled capsules. Liquid-fill hard gelatin capsule technology was established in the early 1980s as an alternative to soft gelatin capsules and offered a number of specific Advantages such as lower moisture and gas transmission, use of high melting point excipients, plasticizer and preservative-free, lower moisture content, ease of coating, and choice of capsule composition.^[6]

Liquid filling hard gelatin capsules have gained exposure for their ability to increase solubility and bioavailability of poorly aqueous soluble drugs. In drug discovery, about 40% of new drug candidates display low solubility in water, which leads to poor bioavailability. Increasing the aqueous solubility of insoluble and slightly soluble drugs is major importance, because most of the newly developed drugs are highly lipophilic in nature and its analysis are mainly carried out using organic solvents like methanol, chloroform, ethanol, benzene, acetone, toluene, carbon tetrachloride, diethyl ether, and acetonitrile. Most of these organic solvents are toxic, volatile, and costlier.^[7]

The main aim of the present study was to improve the solubility and bioavailability Candesartan cilexetil by the technique liquid filling hard gelatin capsules in improving the dissolution profile of the Candesartan cilexetil.

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This review gives a complete overview, and special attention has been paid to formulation design, evaluation and little emphasis on application of liquid filling hard gelatin capsules.

MATERIALS AND METHODS

Materials

Candesartan cilexetil, sodium lauryl sulfate (SLS) was purchased from Fisherscientifics, mumbai. Polyvinyl pyrrolidone was purchased from Moly chem, mumbai. Polyethylene glycol (PEG) was purchased from Lobachemine, mumbai. Propylene glycol (PG) was purchased from Loachimine, mumbai. Ethanol was purchased from Fisherscientifics, mumbai. Sodium hydroxide was purchased from Merck Specialities, mumbai. Potassium di hydrogen phosphate was purchased from Merck Specialities, mumbai.

Drug and excipient compatibility studies

Drug and various physical mixtures were analyzed with infrared radiation spectrophotometer by employing Kbr pellet method. The samples were scanned within the wave number 251 nm region ranges from 500 to 3500 cm^{-1} .^[8]

Saturation solubility of candesartan cilexetil

In order to find out appropriate solvent with good solubilizing capacity of Candesartan cilexetil, the saturation solubility of Candesartan cilexetil was investigated in some solvents like buffers, surfactants and ethanol with buffer combinations. An excess amount of Candesartan cilexetil was added to each solvent and it was allowed to saturation and the samples were centrifuged up to 15 min then the solution was filtered through membrane filter (0.45 μm) and absorbance was observed at 251 nm using ELICO ultraviolet (UV) visible spectrophotometer.^[9]

Preparation of the liquid filling formulation

Liquid filling formulations were prepared as per formulae given in Table 1. Initially, PG and PEG-400 were taken into small beaker and mixed well. Polyvinylpyrrolidone (PVP) K-30 and SLS were then added. Accurate amount of Candesartan cilexetil was weighed according to formulae and transferred into this beaker and mixed thoroughly. It was followed by the addition of ethyl alcohol and 4.8 acetate buffers to dissolve the drug completely. The prepared formulation was sonicated for 10 min in order to remove any entrapped air. The weight of liquid ingredients like

ethyl alcohol, PG, PEG-400 was converted to volume from their density values. The “0” sized hard gelatin capsules were taken and separated the cap and body. Each capsule body was filled by injection with 0.7 ml of the respective formulation was filled up to 75% of its total volume. The capsule body and cap was fully joined and sealed the capsule with gelatin by banding of body and cap to prevent the leakage of contents.^[10]

Evaluation tests for capsulatable mixtures containing candesartan cilexetil finished formulations

Appearance

Appearance is one of the most important of liquid filling formulations. All the formulations were evaluated for clarity by visual appearance.

pH

The developed formulations were evaluated for pH using Elico pH meter and estimations carried out in triplicate.

Rheological studies

Viscosity of all the formulations was measured using a Brookfield viscometer. The formulations were taken into a small volume adapter mounted with spindle SE-18. The viscosity measurements were made in triplicate using fresh samples each time at room temperature.

Content uniformity

Determined the content of active ingredient in each of 10 capsules taken at random using the capsules comply with the test. Not >1 of the individual values thus obtained is outside the limits 85-115% of the average value and none is outside the limits 75-125%.

Characterization of finished capsules

Average weight

Capsules were filled with formulations and determined the average weight of the capsules.

Methods

1. Weighed an intact capsule.
2. Open the capsule without losing formulation of the shell and removed the contents as completely as possible.
3. Weighed the capsule shell.
4. The weight of the contents is the difference between the weights.

Table 1: Composition of candesartan cilexetil liquid filling hard gelatin capsules

| Ingredients | Formulations | | | | | | | | | | | |
|----------------------------|--------------|------|------|------|-----|------|------|------|------|------|------|------|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
| Candesartan cilexetil (mg) | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 69 | 69 |
| SLS (mg) | — | 50 | 100 | 150 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| Ethanol (ml) | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 |
| Water (ml) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| PEG-400 (ml) | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 1.3 | 1.7 | 2.2 |
| Polyvinylpyrrolidone (k30) | 1.00 | 1.00 | 1.00 | 1.00 | 1.0 | 1.00 | 1.25 | 1.50 | 1.75 | 1.75 | 1.75 | 1.75 |
| PG (ml) | 5.2 | 5.17 | 5.12 | 5.07 | 5.0 | 5.0 | 4.78 | 4.54 | 4.30 | 5.3 | 4.8 | 4.3 |

SLS: Sodium lauryl sulfate, PEG: Polyethylene glycol, PG: Propylene glycol

- Repeated the procedure with further 19 capsules selected at random.
- Determined the average weight limit.

Drug content

The amount of drug present in each capsule was estimated by UV spectrophotometric method. The contents present in each capsule were withdrawn, suitably diluted with ethanol, filtered and analyzed at wavelength 251 nm. The same procedure is applied on another 9 capsules.

Disintegration test

For performing disintegration test on capsules, the tablet disintegration test apparatus is used but the guiding disc was not be used except that the capsules float on top of the water. One capsule is placed in each tube which is then suspended in the beakers to move up and down, and the results were noted at complete disintegration of capsule shell. The disintegration test determines for capsules disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions.^[11]

Percentage moisture absorption test

The capsules were collected, weighed accurately and placed in desiccators containing a saturated solution of sodium chloride to keep the desired constant humidity. The liquid filled capsules were collected every day, and the weight was observed. The same procedure was followed for 1 week. The percentage moisture absorption was calculated by using the formula.

$$\text{PMA} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100^{12}.$$

In vitro drug release studies

Dissolution studies were carried out using United States Pharmacopeia XXIII (paddle method) dissolution test apparatus using 900 ml polysorbate (0.35%) 6.5 phosphate buffers as dissolution medium. A temperature $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and a rotation speed of 100 rpm were maintained. Dissolution studies were performed; Samples of 5 ml were withdrawn at predetermined time intervals over a period 1 h. And the samples were filtered. The sample removed was replaced with the same volume of fresh dissolution medium in order to maintain constant dissolution medium. The filtered samples were analyzed at 251 nm using UV-visible Elico spectrophotometer.^[13]

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy studies

Samples were analyzed using a Fourier transform infrared spectroscopy (FTIR). This study was useful for the evaluation of physicochemical compatibility and interactions. The FTIR spectrum of pure Candesartan cilexetil has characteristic peaks of asymmetric C-O-C stretching at 1751.88 cm^{-1} , symmetric C-O-C stretching at 1074.31 cm^{-1} , C-O stretching-H of plane bending at 1031.89 cm^{-1} , and C = O stretching at 1751.88 ,

C-H out of plane bending at 745.50 cm^{-1} . The FTIR studies for Candesartan liquid formulation and Candesartan pure drug have two similar peaks in both spectrums. They are O-H bending, C-H stretching at 1038.44 cm^{-1} , asymmetric C-O-C stretching at 1245.92 cm^{-1} . And along with that some characteristic peaks of excipients like C-H stretching of ethanol at 2874.42 , O-H stretching at 3355.28 cm^{-1} etc. Hence, it was concluded that there was no interaction between Candesartan cilexetil and excipients used in the formulation as the functional groups.^[14]

Solubility studies

The solubility study of candesartan was conducted in different surfactants such as Tween-20, Tween-80, Span80, and SLS. The drug was found to be sparingly soluble in all these surfactants except SLS. The solubility of the drug was found to be more in SLS ($144.51\text{ }\mu\text{g/ml}$) compared to other surfactants. To study the influence of concentration of surfactant on solubility of the candesartan, different concentrations of surfactant SLS ranging from 0.75 to 2.5 (%w/w) were employed. The solubility was found to be dependent on the concentration of SLS. Good positive correlation ship was observed between the concentration of surfactant and solubility of candesartan. More solubility was observed in presence of 2.5%w/v solution. Hence, same concentration was selected further studies.

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Characterization of capsulatable mixtures containing candesartan cilexetil finished formulations

p^H

p^H is an important parameter for liquid filling formulations. The two areas of critical importance are the effect of p^H , on solubility and stability. The P^H of encapsulated formulation should in between 2.5 and 7.5, because more acidic p^H causes hydrolysis of capsule shell, and more alkaline p^H causes tanning of the gelatin shell it leads to maybe reduce the solubility. The results are given in Table 2. The p^H values were obtained between the ranges of 5.3-5.8. Thus, these capsulatable mixtures were found to be suitable to fill into hard gelatin capsules. Obtained values were within the limits, so test was passed.

Rheological studies

The rheological parameters observed from the formulations containing different concentrations of SLS (0-5%), PVP (10-17.5%) and PEG (15-25%). The formulations followed Newtonian type of

flow. The viscosity was found to be increased with the concentration of PVP. It may be due to the thickening effect of the polymer on possible hydration of the aqueous polymer PVP.

The viscosity was found to be increased with the concentration of PEG.

Viscosities of all the formulations were found to be in the range between 1.38 and 8.7 Cp. The acceptable viscosity for capsulatable mixture should be in between 0.222 and 3000 Cp. Thus, these values were found to be suitable to fill into hard gelatin capsules. The results are given in Table 2.

Content uniformity

The capsules comply with the test if not >1 of the individual values thus obtained is outside the limits 85-115% of the average

Table 2: Physical parameters observed from the capsulatable mixtures containing candesartan cilexetil

| Formulations | Appearance | pH | Content uniformity (%) | Viscosity (c _p) |
|--------------|-----------------|-----------|------------------------|-----------------------------|
| F1 | Colorless clear | 5.8±0.002 | 99.56±0.005 | 17.6±0.2 |
| F2 | Colorless clear | 5.7±0.004 | 99.42±0.008 | 17.15±0.4 |
| F3 | Colorless clear | 5.5±0.001 | 99.35±0.004 | 15.46±0.3 |
| F4 | Colorless clear | 5.7±0.003 | 99.18±0.006 | 13.3±0.5 |
| F5 | Colorless clear | 5.5±0.001 | 99.33±0.008 | 19.5±0.2 |
| F6 | Colorless clear | 5.5±0.001 | 99.25±0.002 | 19.5±0.4 |
| F7 | Colorless clear | 5.6±0.002 | 99.35±0.004 | 13.53±0.1 |
| F8 | Colorless clear | 5.7±0.02 | 99.62±0.005 | 14.15±0.3 |
| F9 | Colorless clear | 5.54±0.03 | 99.15±0.008 | 15.23±0.4 |
| F10 | Colorless clear | 5.4±0.001 | 99.85±0.005 | 17.3±0.2 |
| F11 | Colorless clear | 5.3±0.002 | 99.35±0.002 | 15.69±0.3 |
| F12 | Colorless clear | 5.4±0.04 | 99.62±0.007 | 15.23±0.5 |

value and none is outside the limits 75-125 per content. The results were varied from 99.15% to 99.85% as shown in Table 2. The obtained results are within the limits so passed the test.

Studies on characterization of finished capsules

The hard gelatin capsules were filled with the capsulatable mixture as these mixtures satisfied the preliminary requirements. The finished capsules were subjected to various quality control tests.

Average weight

Prepared formulations were subjected to weight variation test as per I.P. the acceptance criteria for weight variation test is as follows.

The results are given in Table 3. The observed weight variation was found to be within the acceptable range 629.9 ± 0.006-695.4 ± 0.006 and thus all the finished capsules satisfied the weight variation requirement.

Drug content

The content of active ingredient test was determined from 20 capsules which were selected randomly. As per I.P requirement, the limits are between 90% and 110% of labeled claim. The observed drug content values are found to be between 96.39 and 99.48%. The observed data indicated that the finished capsules satisfied the drug content requirement. The results are shown in Table 3.

Disintegration test

The disintegration test determines for capsules disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions, According to Indian pharmacopeia, disintegration time for the hard gelatin capsules was 30 min. Disintegration time for all the formulations was varied from the range between 20 and 30 min. For all the formulations, disintegration time is depicted in Table 3. The dosage form satisfied the disintegration requirement.

In vitro drug release studies

All the dissolution studies were carried out in triplicate and each case mean values and standard deviation values were calculated.

Table 3: Physical characters of hard gelatin capsules filled with capsulatable mixtures containing candesartan cilexetil

| Parameters | Average weight (mg) | Disintegration time (min) | Absorbed moisture content (%) | Drug content (%) |
|------------|---------------------|---------------------------|-------------------------------|------------------|
| F1 | 683.3±0.002 | 23±0.04 | 17.17±0.05 | 98.62±0.004 |
| F2 | 660.9±0.003 | 25±0.06 | 19.6±0.04 | 97.69±0.003 |
| F3 | 695.4±0.006 | 22±0.02 | 18.2±0.01 | 98.92±0.008 |
| F4 | 661.2±0.008 | 26±0.07 | 17.25±0.02 | 98.81±0.009 |
| F5 | 674.13±0.02 | 24±0.02 | 17.29±0.002 | 97.39±0.007 |
| F6 | 674.12±0.06 | 28±0.02 | 17.2±0.002 | 96.39±0.002 |
| F7 | 629.9±0.002 | 25±0.05 | 13.9±0.001 | 98.73±0.003 |
| F8 | 653.9±0.003 | 26±0.03 | 19.8±0.007 | 97.69±0.005 |
| F9 | 652.2±0.004 | 28±0.07 | 17.1±0.005 | 98.31±0.006 |
| F10 | 674.12±0.004 | 29±0.03 | 16.8±0.007 | 99.48±0.001 |
| F11 | 629.9±0.006 | 25±0.04 | 18.2±0.004 | 97.73±0.005 |
| F12 | 653.9±0.028 | 26±0.02 | 16.1±0.006 | 96.69±0.002 |

In vitro dissolution studies were carried out for the formulations prepared with 0-2% concentrations of SLS and the results are shown in Figure 1. These studies revealed that the concentration of surfactant significantly influences the dissolution rate of candesartan and 2%w/w of SLS was found to be suitable for enhancing the dissolution rate of candesartan.

In vitro dissolution studies were carried out for the formulations prepared with 10-17.5% concentrations of PVP and the results are shown in Figure 2. The concentration of PVP significantly influences the dissolution rate of candesartan, and 17.5%(w/w) of PVP was found to be suitable for enhancing the dissolution rate of candesartan. *In vitro* dissolution studies were carried out for the formulations prepared with 15-25% concentrations of PEG and the results are shown in Figure 3. The drug release with 15% PEG was significantly higher than other concentrations of PEG formulations. Time required for the dissolution of 50% (T₅₀) and the 90% (T₉₀) of the labeled claim were observed for all the formulations and reported in Tables 4-6.

Moisture absorption studies

The properties of the active pharmaceutical ingredient (API) and suitable excipients are studied to check whether it is a good candidate for liquid filling and evaluated so that neither the API nor excipient should cause the gelatin shell to gain or lose excessive moisture. Due to the presence of 12-15% moisture, plasticizer effect can be maintained for gelatin in hard gelatin capsules. So when a hygroscopic material is filled into the capsule that could extract moisture from the shell thereby inducing embrittlement.

Prepared formulations having the candesartan drug is totally hydrophobic; so no problem about embrittlement of capsule shell. However, the components of capsulatable mixture like PEG, PVP are hygroscopic and are able to absorb moisture from the surrounding environment. Hence, there is a need to determine the moisture content as it may affect the physical and chemical stability of the capsules. The moisture absorption studies were found to be in an acceptable range for all formulations indicating their stability.

If the moisture content absorption is increased, it may interfere in filling capacity of capsule shell. All the formulations of absorbed moisture content were found to be in the range between 11.9 ± 0.001 and 15.8 ± 0.008 . The results were found to be

within the limits, so the test was passed. Obtained results are given in Table 3.

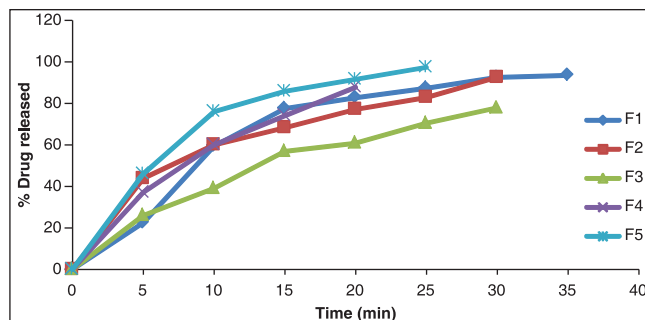


Figure 1: *In vitro* release data of hard gelatin capsules filled with capsulatable mixtures containing different concentration of surfactant sodium lauryl sulfate (0-2%)

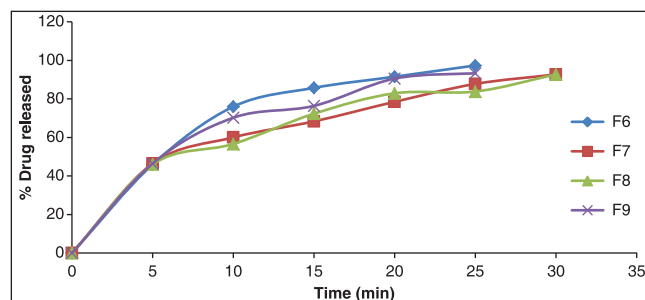


Figure 2: *In vitro* release profiles of hard gelatin capsules filled with capsulatable mixtures containing different concentrations of Polyvinylpyrrolidone (10-17.5%)

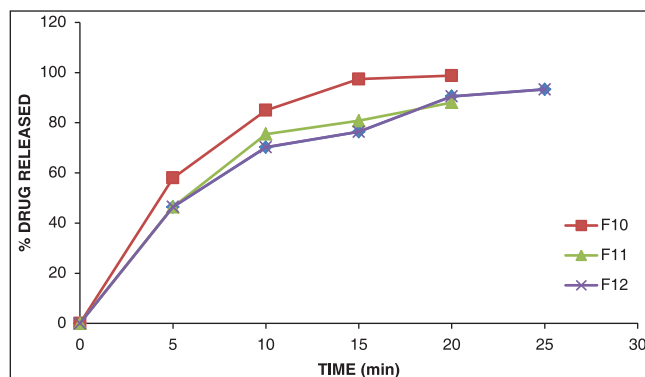


Figure 3: *In vitro* release profiles of hard gelatin capsules filled with capsulatable mixtures containing different concentrations of polyethylene glycol (15-25%)

Table 4: Release kinetics of hard gelatin capsules filled with capsulatable mixtures containing different concentrations of surfactant SLS (0-2%)

| Formulation | Correlation coefficient values | | | Half life | Shelf life |
|-------------|--------------------------------|-----------------|-------------------------------|-----------------------|-----------------------|
| | Zero order (r) | First order (r) | K values (min ⁻¹) | T ₅₀ (min) | T ₉₀ (min) |
| F1 | 0.8537 | 0.9906 | 0.0841 | 8.2 | 27.3 |
| F2 | 0.8349 | 0.9809 | 0.0798 | 8.7 | 28.8 |
| F3 | 0.9339 | 0.9948 | 0.049 | 13.9 | 46.1 |
| F4 | 0.9870 | 0.9924 | 0.0985 | 7.0 | 23.3 |
| F5 | 0.8432 | 0.9919 | 0.1362 | 5.1 | 16.8 |

SLS: Sodium lauryl sulfate

Table 5: Release kinetics of hard gelatin capsules filled with capsulatable mixtures containing different concentrations of PVP (10-17.5%)

| Formulation | Correlation coefficient values | | | Half life | Shelf life |
|-------------|--------------------------------|-----------------|-------------------------------|-----------------------|-----------------------|
| | Zero order (R) | First order (R) | K values (min ⁻¹) | T ₅₀ (min) | T ₉₀ (min) |
| F6 | 0.8432 | 0.9919 | 0.313 | 5.1 | 16.8 |
| F7 | 0.982 | 0.9904 | 0.0843 | 7.9 | 26.4 |
| F8 | 0.8304 | 0.9853 | 0.0836 | 8.0 | 26.7 |
| F9 | 0.854 | 0.9914 | 0.1105 | 6.3 | 20.8 |

PVP: Polyvinylpyrrolidone

Table 6: Release kinetics of hard gelatin capsules filled with capsulatable mixtures containing different concentrations of PEG (15-25%)

| Formulation | Correlation coefficient values | | | Half life | Shelf life |
|-------------|--------------------------------|-------------|----------|-----------------------|-----------------------|
| | Zero order | First order | K values | T ₅₀ (min) | T ₉₀ (min) |
| F10 | 0.849 | 0.9902 | 0.513 | 3.1 | 10.2 |
| F11 | 0.874 | 0.982 | 0.113 | 6.1 | 20.4 |
| F12 | 0.854 | 0.9914 | 0.254 | 6.3 | 20.8 |

PEG: Poly ethylene glycol

CONCLUSION

The formulation containing SLS-(2%), ethanol-(0.9), 4.8 acetate buffer-(0.1%) PVP-(17.5%), PEG-(15%), and PG-(53.4%) offered higher percentage of drug release.

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