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Formulation & Evaluation of Effervescent Tablet of Verapamil Hydrochloride

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The chief aim of the present investigation is to study the Formulation & Evaluation of Effervescent Tablet of Verapamil Hydrochloride. The floating tablets of verapamil hydrochloride were prepared by direct compression technique. For each tablet formulation, drug, HPMC-K15M, karaya gum, sodium bicarbonate, and diluents were blended homogeneously for 10 min followed by addition of magnesium stearate. The total weight of each tablet was 300 mg. The amount of karaya gum used was in the range of 40–90 mg, whereas HPMC was used in the range of 20-40 mg. The powder mixture was further mixed for 5 min in a mortar. The resultant mixture was compressed into tablets using a Rimek rotary tablet machine. After preparation, the formulations were evaluated by various parameters. The friability of the tablet formulation varied between 0.3 ± 0.0063 to 0.59 ± 0.0076%. The weight variation of prepared tablet formulation complies with USP limits. The thickness was found to be in the range of 4.1 ± 0.48 to 4.2 ± 0.76 mm. The assay for drug content varied between 96.53 ± 0.36 to 102.03 ± 0.52%. The B1, B5, B6, B9, and B10 exhibited more than 75% drug release at 12 h. The B1 exhibited a maximum of 30 % drug release in the 1st hour and constant release for almost up to 12 h. B8 showed the least drug release among all other formulations; this may be due to the formation of a thick gel barrier on the tablet. Tablets were prepared by direct compression. Technological characteristics of floating tablets were within the Pharmacopoeial limit. Tablets floated for more than 8 h. Complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations.

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1. INTRODUCTION

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration [1]. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres [2-5].

2. MATERIALS AND METHODS

2.1 Formulation of Effervescent Floating Tablets

The floating tablets of verapamil hydrochloride were prepared by direct compression technique. For each tablet formulation, drug, HPMC-K15M, karaya gum, sodium bicarbonate, and diluents were blended homogeneously for 10 min followed by addition of magnesium stearate. The total weight of each tablet was 300 mg. The amount of karaya gum used was in the range of 40–90 mg, whereas HPMC was used in the range of 20-40 mg. The powder mixture was further mixed for 5 min in a mortar. The resultant mixture was compressed into tablets using a Rimek rotary tablet machine. Thirteen formulations were prepared by changing the amount of the ingredients as shown in table [6-7].

2.2 Technological Characteristics of Floating Tablets [8]

2.2.1 Weight variation test

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight. For the tablets of average weight 350 mg, the % deviation allowed is ± 5 %.

$$\% \text{ deviation} = \frac{\text{Average weight of tablet} - \text{individual tablet weight}}{\text{Average weight of tablet}} * 100$$

2.2.2 Friability

Ten tablets were weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was calculated using the equation:

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F is percentage friability, W is the initial weight of tablet and W_t is the final weight of tablets after revolutions.

2.2.3 Hardness

The hardness of core tablets was measured using a hardness tester. A total of five tablets from each formulation were taken for the study and the average of the three is reported. It is expressed in kg.

2.2.4 Thickness and diameter

Thickness and diameter of the tablets were determined by using Mitutoyo micrometer screw gauge. The average of five tablets from each formulation was taken. It is expressed in millimeter.

2.2.5 Uniformity of drug content

Drug content uniformity was determined by randomly selecting 5 tablets were powdered. The quantity equivalent to single dose of the drug was dissolved in HCl buffer solution, pH 1.2 for 5 hours with occasional shaking and diluted to 100 ml with buffer. After filtration to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with the buffer. The absorbance was measured at the required λ_{max} using a UV visible spectrophotometer. The experiments were carried out in triplicate for all formulations and average values were recorded.

The drug content was calculated using the following equation:

% Drug content = conc. (µg/ml) × Dilution factor × 100/ 50

2.2.6 Drug-excipient compatibility studies

2.2.6.1 Fourier transform infra red spectroscopy (FT-IR)

In order to evaluate the integrity and compatibility of the drug in the formulation, drug-excipient interaction studies were performed. Pure drug and optimized formulations were analyzed by Fourier transform infra-red (FTIR) spectroscopy. FTIR spectra of pure drug and its formulations were obtained by a FT-IR Shimadzu 8400S (Japan) spectrophotometer using the KBr pellet method. The samples were scanned from 400 to 4,000 cm^{-1} wave number.

2.2.6.2 Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed on pure sample of drug and its formulation. Calorimetric measurements were made with empty cell (high purity alpha alumina discs) as the reference. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C min^{-1}. The energy was measured as Joules per kilocalorie [9].

2.2.6.3 In vitro floating studies [10]

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP dissolution apparatus type-II (basket) using 900 ml of 0.1 N HCl buffer solutions at 100 rpm at 37 ± 0.5°C. The time required for the formulation to rise to the surface of the dissolution medium and the duration for which the formulation constantly floated on the dissolution medium were noted as floating lag time and total time, respectively.

2.2.7 Water uptake studies [11]

The swelling of the polymers was measured by their ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffers at 100 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. At regular time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as:

$$WU\ (\%) = \frac{\text{Weight of Swollen tablet- Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

3. RESULTS AND DISCUSSION

3.1 Technological Characteristics of Floating Tablets

The hardness of prepared floating tablets ranged between 4.1 ± 1.23 to 6.1±0.306 Kg depending upon the mixture of the polymer used. The friability of the tablet formulation varied between 0.3 ± 0.0063 to 0.59 ± 0.0076%. The weight variation of prepared tablet formulation complies with USP limits. The thickness was found to be in the range of 4.1 ± 0.48 to 4.2 ± 0.76 mm. The assay for drug content varied between 96.53 ± 0.36 to 102.03 ± 0.52%.

Table 1. Formulation chart of effervescent floating Verapamil hydrochloride tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Verapamil Hydrochloride	120	120	120	120	120	120	120	120	120	120	120	120	120
Karaya Gum	40	40	40	40	70	70	70	70	70	90	90	90	90
HPMC K15 M	20	40	30	30	20	40	20	40	30	20	40	30	30
Sodium Bicarbonate	20	20	10	30	10	10	30	30	20	20	20	10	40
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	70	50	70	50	60	40	40	20	40	30	10	30	00
Total weight	300	300	300	300	300	300	300	300	300	300	300	300	300

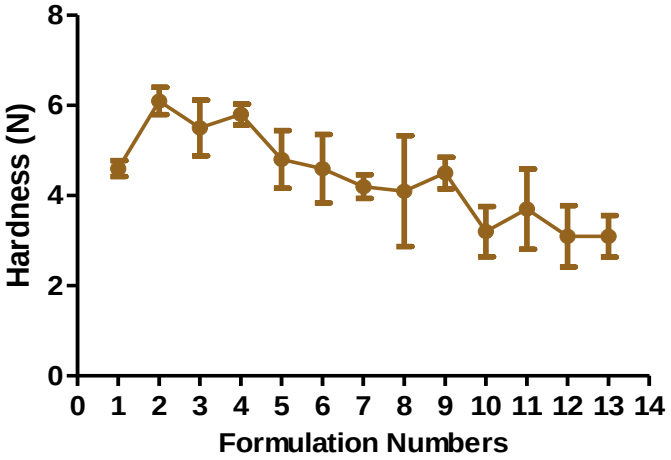

Fig. 1. Effect on Hardness of Different formulations

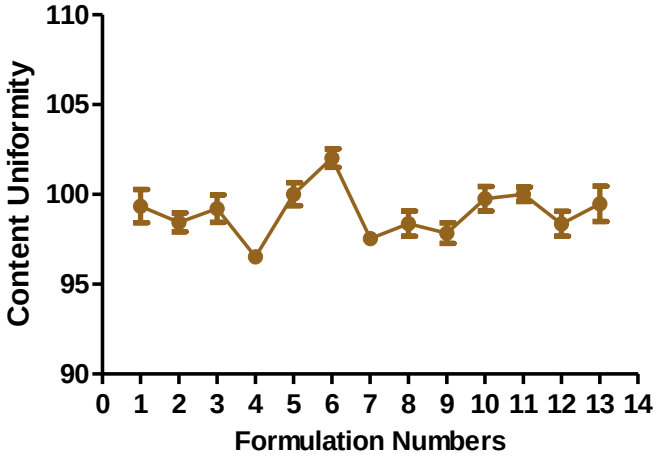

Fig. 2. Effect on Content Uniformity of Different formulations

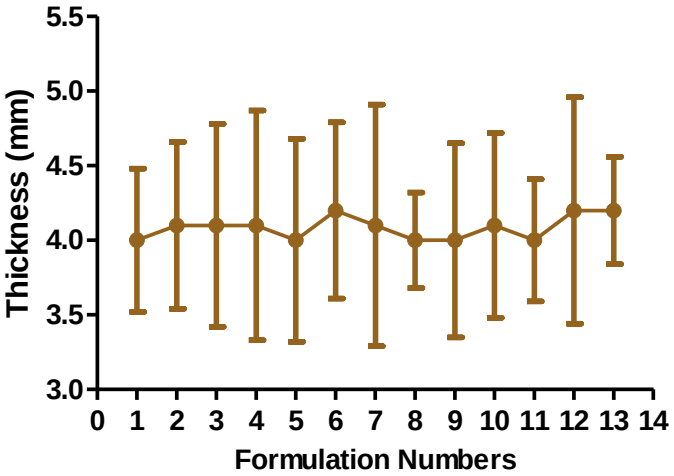

Fig. 3. Effect on Thickness of Different formulations

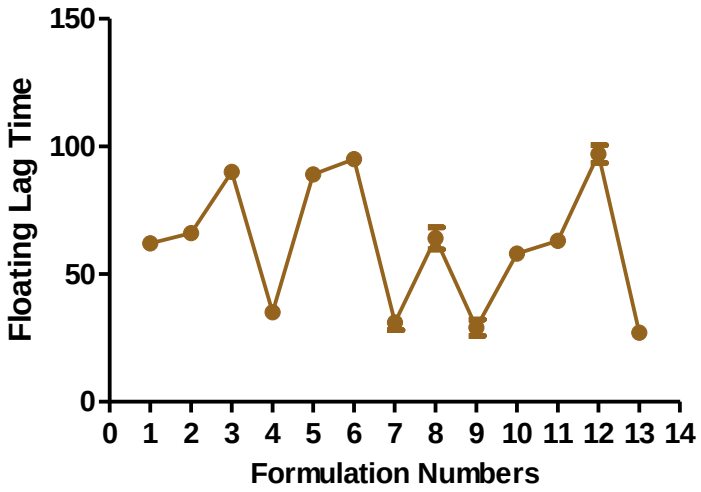

Fig. 4. Effect on Floating lag time of Different formulations

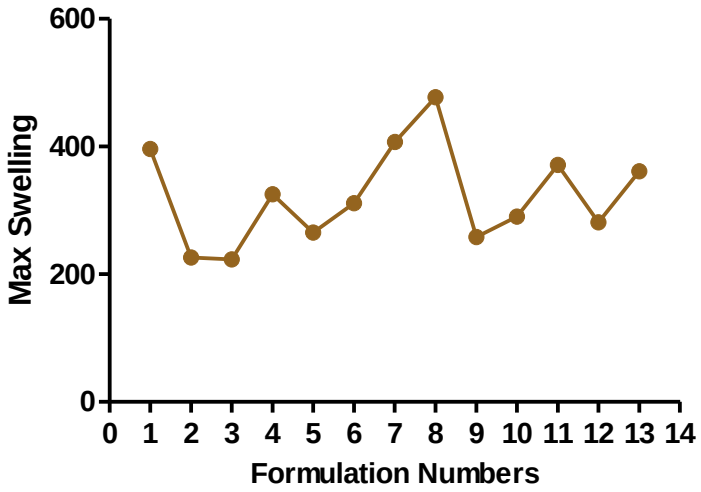

Fig. 5. Effect on Max Swelling of Different formulations

Table 2. FT-IR Spectral data of effervescent floating tablet of Verapamil hydrochloride (B1) and Verapamil hydrochloride pure drug

Functional groups	Frequency of pure drug (cm^{-1})	Frequency of formulation (cm^{-1})
C-H Stretching Vibrations of methyl and methylene groups	3030.5-2860	3051.49–2789.16
C-H stretching Vibrations of the methoxy group	2840	2843.17
C-O stretching Vibrations of the aromatic ethers	1262	1255.70
sharp weak bond due to C=N stretching vibrations of the alkyl nitrile	2236	2235.57
Skeletal stretching Vibrations of the benzene ring	1607, 1518	1599, 1518

3.2 Fourier Transform Infrared Spectroscopy (FT-IR)

The spectrum was measured in the solid state as Potassium bromide dispersion. The bands were recorded using the FT-IR technique. FT-IR spectral study revealed that similar characteristic peaks appear with minor differences, for the pure drug and drug formulation. Hence it was confirmed that no chemical interaction had taken place between the drug and the polymer used.

3.3 Differential Scanning Calorimetry (DSC)

DSC is a fast and reliable method to screen drug and excipient compatibility, and to provide maximum information about the possible interactions. DSC study was carried out for Verapamil hydrochloride and its formulation B1. Thermogram of pure drug shows a sharp endothermic peak at 138.25°C, which corresponds to its melting point. Matrix tablet formulation B1 also showed endothermic peak at 139.53°C, which corresponds to the melting point of the drug. The evaluation of thermograms obtained from DSC revealed no interaction between the drug and the excipients [12].

3.4 *In vitro* Buoyancy Studies

As the density of the tablet fell below 1g/ml, the tablet became buoyant. Karaya gum with HPMC produced tablets with good gel strength, entrapping CO_2 gas within and thereby imparting stable and persistent buoyancy. The system need to float in a few minutes after contact with gastric fluid, to prevent the dosage form from being pushed into the small intestine together with food. The results demonstrated that the time taken by the system to float in the medium, decreased with increasing amount of effervescent agent and increased with increasing levels of Karaya gum, which was true in B [13]. The higher amount of effervescent agent caused faster and higher CO_2 generation. Thus, Sodium bicarbonate was essential to achieve optimum buoyancy. In general, gastric emptying time was 4h. The extended gastric residence time of the drug in the stomach caused increased absorption due to the fact that the proximal part of the intestine was the main absorption site for Verapamil hydrochloride [14].

3.5 Water Uptake Studies

There was rapid increase in percentage swelling of the B4, B6, and B7 at 1 h. B8 showed a gradual increase in percentage of swelling at the end of 8 h. The increase in the concentration of Karaya gum retarded the water uptake during the first hour. B2, B3, and B5 showed a decrease at the end of 8 h. There was no significant difference observed in the swelling property by varying the concentration of Sodium bicarbonate, but less concentration of lactose in B8 showed maximum swelling ($p \geq 0.05$). As described by Seipmann and Peppas diffusion of drug significantly depends on the water content of the tablet. This may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling to the system. Also, this higher water content could predict the higher penetration of the gastric fluid into the tablet, leading to faster carbon dioxide gas generation, and thus reduction in the floating lag time. Consequently, faster and higher swelling of the tablet led to an increase in the dimensions of the tablet, leading to increasing the gel barrier and thus decreasing diffusion rates.

Table 3. DSC thermogram data of effervescent floating tablet of Verapamil hydrochloride (B1) and Verapamil hydrochloride pure drug

Drug and formulation	T_O(°C)	T_m(°C)	T_C(°C)	Melting range(°C)
Verapamil Hydrochloride	131.20	139.53	145.73	14.10
Formulation B1	130.99	138.25	144.85	13.86

T_O - Onset of melt, T_m - Melting point, T_C - Completion of melt,

Table 4. Effect of Sodium bicarbonate on onset and duration of floatation of effervescent floating tablet of Verapamil hydrochloride (B1)

Amount of sodium bicarbonate (mg)	Onset of floating (s)	Duration of floating (h)
10	92±3.86	16±0.81
20	62±2.96	21±0.36
30	32±2.50	24±0.69
40	27±0.05	18±0.75

3.6 *In vitro* Drug Release Studies

The B1, B5, B6, B9, and B10 exhibited more than 75% drug release at 12 h. The B1 exhibited a maximum of 30 % drug release in the 1st hour and constant release for almost up to 12 h. B8 showed the least drug release among all other formulations; this may be due to the formation of a thick gel barrier on the tablet. As the thickness of the gel barrier increased, the drug took more time to diffuse through it; this was observed in other formulations which showed higher swelling index. However, this was not true in case of B1 because of the presence of higher concentration of lactose. The controlled release of drug from the formulations might be because of the diffusion of release medium into the matrix, which in turn would have caused drug diffusion out of the tablets.

3.7 Mathematical Model Fitting of Obtained Drug Release Data

The *in vitro* drug dissolution profiles were fitted to various models and release data was analyzed on the basis of Korsmeyer-Peppas equation and Higuchi kinetics. The diffusion exponent ranges from 0.3771–0.6997. The release rates *k* and *n* values of each model were calculated by PCP disso v2.08 software. Co-efficients of correlation (R^2) were used to evaluate the accuracy of the model fitting. On calculating and comparing R^2 values for, Korsmeyer-Peppas, Matrix, and other models, B4, B5, B7, and B12 gave a good fit to the Matrix model, and the remaining formulations best fitted the Korsmeyer-Peppas model. B1, B4 and B7 exhibited Fickian release and other formulations showed non- Fickian or anomalous release. B4 and B7 best fitted to the matrix model with Fickian release; B5 and B12 best fitted to the matrix model with non-Fickian release. If the value of „*n*" in Korsmeyer-Peppas is 0.5 or less, the release mechanism follows a Fickian diffusion, and for anomalous or non-Fickian, release the release is mainly by diffusion with *n* values between 0.5-1. This model was used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well- known or, when more than one type of release phenomenon could be involved. The fundamental of diffusion is based on Fick"s laws, which describes the macroscopic transport of molecules by a concentration gradient.

3.8 Stability Studies

Stability studies were performed for the optimized formulation B1to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25ºC/60% RH, 30ºC/65% RH for 12 months and 40ºC/75% RH for 6 months. There was no significant change in the physical appearance and drug content during the study period. The results of drug content determination during stability testing period are reported in table 5. The drug content in the formulation in long-term storage conditions and accelerated storage conditions along with 95% confidence interval was plotted using Sigmaplot software 12.0. Results showed that changes in the parameters evaluated, were very small and were not significant.

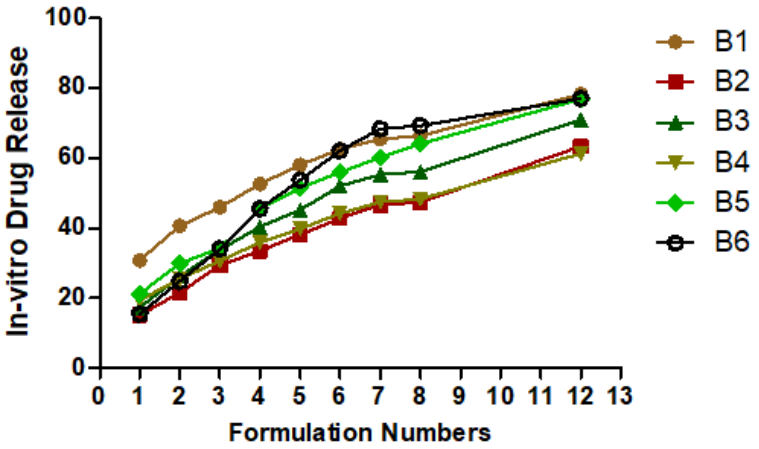

Fig. 6. In-vitro drug release of Different formulations

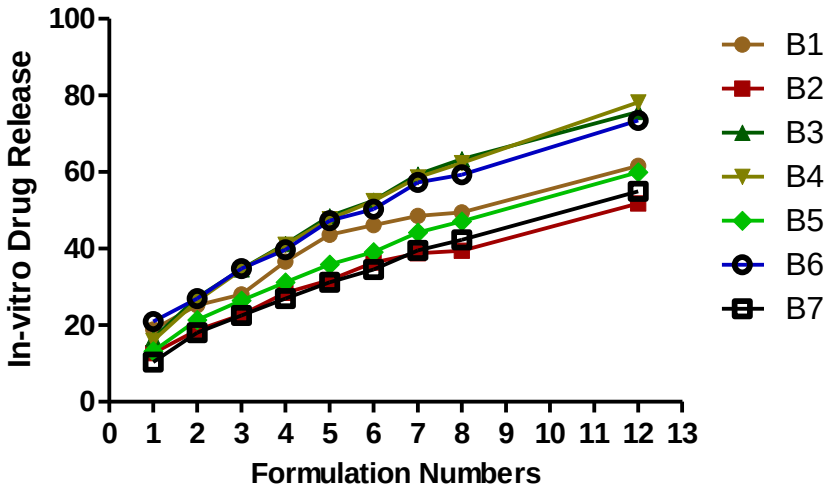

Fig. 7. In-vitro drug release of Different formulations

Table 5. Stability study data of effervescent floating tablet formulation (B1) of Verapamil hydrochloride

Stability condition	Sampling interval (months)	Physical appearance	% Drug content B1 (mean ± S.D*)
25°±2°C/60±5% RH	0	No change	99.35 ± 0.13
	3	No change	99.20 ± 0.11
	6	No change	98.43 ± 0.15
	12	No change	98.35 ± 0.16
30°±2°C/65±5% RH	0	No change	99.35 ± 0.19
	3	No change	99.12 ± 0.12
	6	No change	98.67 ± 0.17
	12	No change	98.13 ± 0.13
40°±2°C/75±5% RH	0	No change	99.35 ± 0.93
	3	No change	98.60 ± 0.79
	6	No change	96.34 ± 0.26

4. CONCLUSION

Tablets were prepared by direct compression. Technological characteristics of floating tablets were within the Pharmacopoeial limit. Tablets floated for more than 8 h. Complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations. The formulations F1, F5, F6, F9, and F10 exhibited more than 75 % drug release at 12 h. The formulation F1 exhibited a maximum of 30 % drug release in the 1st hour and constant release for almost up to 12 h. Based on the *in vitro* evaluation data, formulation F1 was considered as optimized formulation.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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