Research Article

FORMULATION AND EVALUATION OF FOLDING FILM IN A CAPSULE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM OF LOSARTAN POTASSIUM

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ABSTRACT

The main objective of the present study was to prepare the gastro retentive sustained release films enclosed in a capsule. Sustained release films constitute an innovative dosage form that overcomes the problems of frequent dosing and provides a sustained action for a longer period of time and has more gastric retention time due to its flat surface. Design expert 11 trial version has been used for the optimization of formulation by taking amount of ethyl cellulose, amount of PEG and concentration of coating solution of ethyl cellulose in % w/v. as factor A, B and C respectively at two levels which are responsible for the drug release. Sustained release films were prepared by solvent casting method using different polymers like HPMC K4M, HPMC K100M, HPMC 50cps, Ethyl cellulose, and PEG as the plasticizer. The prepared sustained release films were evaluated for various evaluating parameters. The selected formulations were subjected to stability studies at 40 ± 2°C and 75 ± 5% RH for 30 days. All the formulations showed low weight variation with sustained release of drug. The physical properties like tensile strength, folding endurance, and drug content of all the formulations were within the acceptable limits. Sustained release films showed no change in appearance, drug content and dissolution profiles.

Keywords: sustained release film, losartan potassium, gastro retentive, polymers, solvent casting method.

INTRODUCTION

High blood pressure is a major independent risk factor for cardiovascular disease and stroke; Indeed 5.8% of all deaths are directly linked with hypertension. All in all, hypertension is one of the five chronic diseases (psychological illnesses, diabetes, heart disease, asthma), which are responsible for half the expenditure of the health systems.[1] Oral drug delivery systems are more convenient and commonly used method of drug delivery system and are generally considered ideal drug delivery system. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process.[2] The objective of this study is to develop the ideal drug delivery system which will perform as the sustained delivery of drug for the treatment of hypertension. The film in a capsule has a number of advantages of over conventional drug delivery system such as improved efficiency, reduced toxicity, single dose therapy and improved patient compliance.[3] The drugs which are locally active in the stomach, have an absorption window in the stomach or in the upper small intestine.[4] They are unstable in the intestinal or colonic environment, or exhibit low solubilities at high pH values.[5] These limits, promote the development of gastroretentive drug delivery systems (GRDDSs).

Factors affecting GRDDS performance

Formulation factors

The shape of the dosage form is one of the factors that affect its GRT. Six shapes (ring, tetrahedron, cloverleaf, string, pellet, and disk) were screened *in-vivo* for their gastric retention potential.[6] In the case of floating systems, formulation variables such as the viscosity grade of the polymers and their interactions significantly affect floating properties of the delivery system and drug release. Low-viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high-viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.[7]

Idiosyncratic factors

The concomitant intake of food and drugs such as anti-cholinergic (e.g., atropine or propantheline), opiates (e.g., codeine) and prokinetic agents (e.g., metoclopramide and cisapride), may affect the performance of GRDDS. The co-administration of GI motility–decreasing drugs can increase gastric emptying time. On the contrary, these drugs should be contraindicated with mucoadhesive systems because they reduce gastric secretion and induce the drying of mucus membranes.[8]

Biological factors such as gender, age, posture, body mass index, and disease state (e.g., diabetes or Crohn's disease) may also affect gastroretention. For example, women and the elderly show slower gastric emptying than do men and younger subjects. Floating forms appear to be equally likely to remain buoyant anywhere between the lesser and greater curvatures of the stomach. On moving distally, these units may be swept away by the contractile waves that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects. Therefore, patients preferably should not be dosed with a floating drug delivery system just before going to bed.[9] Optimisation was done by 2^3 full factorial design by using design expert trial version 11.[10]

MATERIALS AND METHODS

Materials

Losartan potassium was obtained as the gift sample from Indoco Remedies Limited Mumbai 400098, India. Analytical grade solvents, Ethylcellulose, Eudragit and HPMC (Hydroxy propyl methyl cellulose) of different grade were purchased from S.D.Fine chem Pvt. Ltd, Mumbai.

Method

Solvent casting method was followed to manufacture the sustained release film of losartan potassium. All the polymers selected, drug and excipients were passed through sieve no.60 before using into formulation. Polymers selected for expandable films are: HPMC 15cps, HPMC 50cps, HPMC K100M**,** HPMC K4M**,** Eudragit L100**,** Ethyl cellulose, and Polyethylene glycol.

Steps involved in the manufacture of sustained release films in a capsule

1. First the drug, polymer and other excipients selected were passed through 60-mesh sieve.
2. Required quantity of drug, polymer and excipients were weighed properly and transferred into 20 ml beaker and equal mixture of ethyl alcohol and chloroform were added to it with constant stirring
3. The solution was casted in a petri dish which is 38.5 cm^2 and kept for drying for 24 hours at room temperature.
4. Then coating of ethyl cellulose is done to the films formed and dried.
5. The formed films were cut into smaller films of 3cm x 3cm size then folded in zigzag fashion and enclosed in 0 size capsule.[11]

Optimization

Optimization was done by using Design-Expert 11 trial version software. Total 8 batches were prepared by applying 2^3 factorial design subtype randomized with 0 center points. All the batches were evaluated and different polynomial equations were derived for Cumulative % drug release at 2 hours (Q2), 6 hours (Q6) and 8 hours (Q8). The statistical analysis of the factorial design batches was performed by ANOVA using Design-Expert 11 trial version software.

Table 1: The 2^3 randomized factorial design of formulation with the responses

Run	Factor 1 A:amount of EC mg	Factor 2 B:Amount of PEG ml	Factor 3 C:% wt gain of ... %
1	50	0.25	15
2	100	0.5	15
3	50	0.5	5
4	100	0.25	5
5	50	0.25	5
6	100	0.25	15
7	100	0.5	5
8	50	0.5	15

EVALUATION OF SUSTAINED RELEASE FILMS

1. **Weigh variation of Films**

Sustained release expandable films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of API and excipients.

2. Thickness of Films

By using vernier caliper the thickness of the film was measured at three different places and average of was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of the dose in film.

3. Folding Endurance

Folding endurance is measured by manual repeated folding of the film at the same place till it breaks. The number of times the film is folded without breaking is known as the folding endurance value.[12]

4. Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by applied load at rupture divided by the cross sectional area of the strip as given in the following equation[12]

Tensile strength = Load at failure × 100/film thickness × film width

5. Percent Elongation

When stress is applied to a film sample it stretches and this is referred as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content increases.

% Elongation = Increase in length× 100/ Initial length of film

6. Drug content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity for losartan potassium is 98.5%-101.5%.

7. Surface pH

The film to be tested was placed in a petri dish and was moistened with 0.5 ml of distilled water and kept for 30 seconds. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.[13]

8. Dissolution test

Dissolution test was performed using USPXXII dissolution apparatus-II. 900 ml of pH 1.2 buffer was used as dissolution medium. The temperature was maintained at 37 ± 0.5℃. Rotation of the paddle speed was kept at 50 rpm which simulates the peristaltic movement of the gastro-intestinal tract.

RESULTS

Table 2: Standard calibration curve of Losartan potassium in pH 1.2 buffer

S. No.	Concentration (µg/ml)	Average Absorbance in pH 1.2 buffer (N=6)
1.	3	0.416±0.022361
2.	6	0.7214±0.079598
3.	9	1.0132±0.091489
4.	12	1.2986±0.119486
5.	15	1.7578±0.151584
6.	18	2.0794±0.184275
7.	21	2.388±0.196628
8.	24	2.7342±0.231642
9.	27	3.0296±0.28133
10.	30	3.2452±0.235379

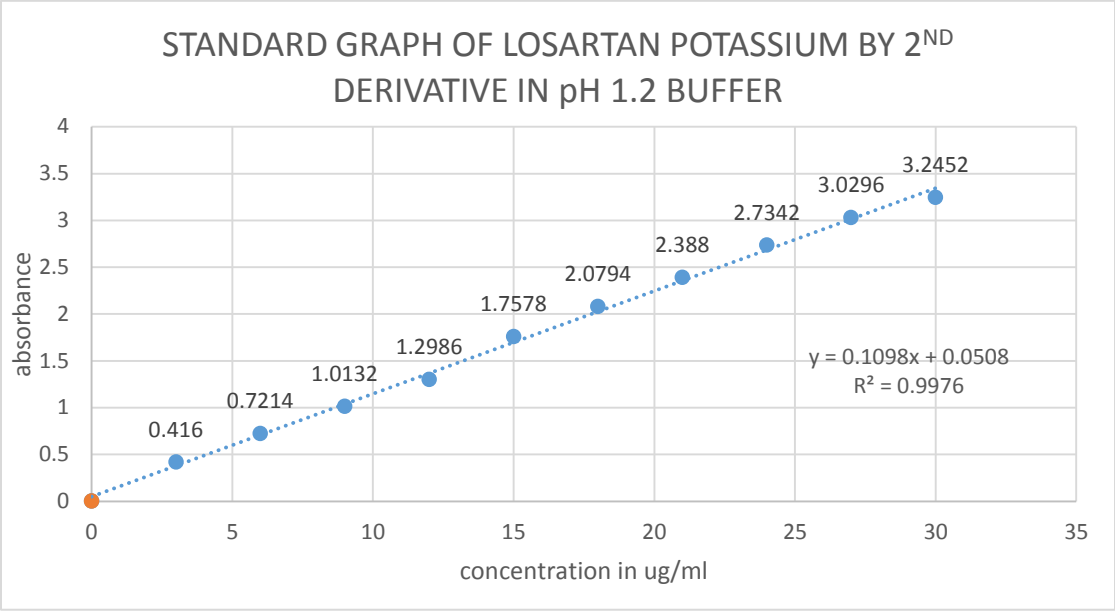

Fig. 1: Standard graph of losartan potassium by 2nd derivative in pH 1.2 buffer

Table 3: Results of various evaluating parameters of Drug and formulation R1 to R8

Run	Amount of ethyl cellulose (mg)	Wt. of the film (Gram)	Thickness (mm)	Folding endurance	Tensile strength (kg/mm^2)	%elongation (%)	% drug content	Surface pH
1	50	0.341 ± 0.019	0.20 ± 0.007	>150	5.140 ± 0.041	5.640 ± 0.049	98.40±0.22	7.1±0.12
2	100	0.470 ± 0.012	0.28 ± 0.005	>150	6.091 ± 0.050	6.667 ± 0.044	98.86±0.24	7.0±0.13
3	50	0.353 ± 0.015	0.21 ± 0.007	>150	5.011 ± 0.048	4.801 ± 0.050	97.45±0.25	6.9±0.12
4	100	0.467 ± 0.014	0.27 ± 0.007	>150	5.901 ± 0.052	6.680 ± 0.051	98.52±0.20	6.8±0.11
5	50	0.356 ± 0.016	0.21 ± 0.009	>150	5.120 ± 0.048	4.750 ± 0.041	98.12±0.21	6.7±0.13
6	100	0.451 ± 0.011	0.29 ± 0.003	>150	6.078 ± 0.051	6.640 ± 0.043	98.36±0.23	7.2±0.11
7	100	0.468 ± 0.013	0.30 ± 0.005	>150	6.041 ± 0.056	6.560 ± 0.053	98.45±0.27	7.1±0.13
8	50	0.364 ± 0.018	0.22 ± 0.009	>150	4.750 ± 0.049	5.401 ± 0.046	98.12±0.28	7.0±0.12

Table 4: *In-vitro* dissolution studies profile of R1 to R8 formulations

Time	%Cumulative Drug Release							
Hrs	R1	R2	R3	R4	R5	R6	R7	R8
1.	13.481±0.052	5.458±0.326	10.245±0.312	4.3476±1.128	7.568±0.820	1.951±0.085	6.214±0.448	7.355±0.764
2.	14.276±0.098	7.605±0.790	15.513±0.746	9.182±1.002	3.130±0.374	5.102±0.504	10.052±1.012	19.610±0.833
3.	21.636±0.728	15.425±0.618	24.254±0.381	12.082±0.138	22.760±1.077	9.126±0.320	16.254±0.379	19.577±1.401
4.	27.335±0.299	20.143±0.064	34.214±0.966	16.340±0.498	28.474±0.636	14.578±0.631	24.158±0.400	26.472±0.858
6.	36.321±0.502	22.562±0.021	52.905±1.249	21.417±0.572	37.397±0.634	20.567±0.647	31.641±1.108	41.214±1.357
8.	41.830±0.020	34.214±0.007	61.235±0.350	38.562±0.654	49.451±0.668	31.215±0.509	43.124±0.516	56.854±1.973
12.	51.555±0.767	46.979±0.106	75.125±0.197	49.254±1.072	62.354±0.706	45.254±0.562	63.713±1.312	77.254±0.338
16.	55.908±1.433	60.456±0.790	86.235±0.674	60.245±1.301	75.558±0.753	61.021±0.219	81.249±0.698	80.125±0.890
20.	88.278±1.589	86.196±0.497	91.124±0.193	75.388±0.895	89.458±0.853	76.325±1.228	95.038±0.998	95.152±0.838
24.	90.688±0.660	95.674±2.007	100.125±1.414	87.245±1.400	101.245±0.987	90.214±1.458	100.838±1.361	97.659±1.077

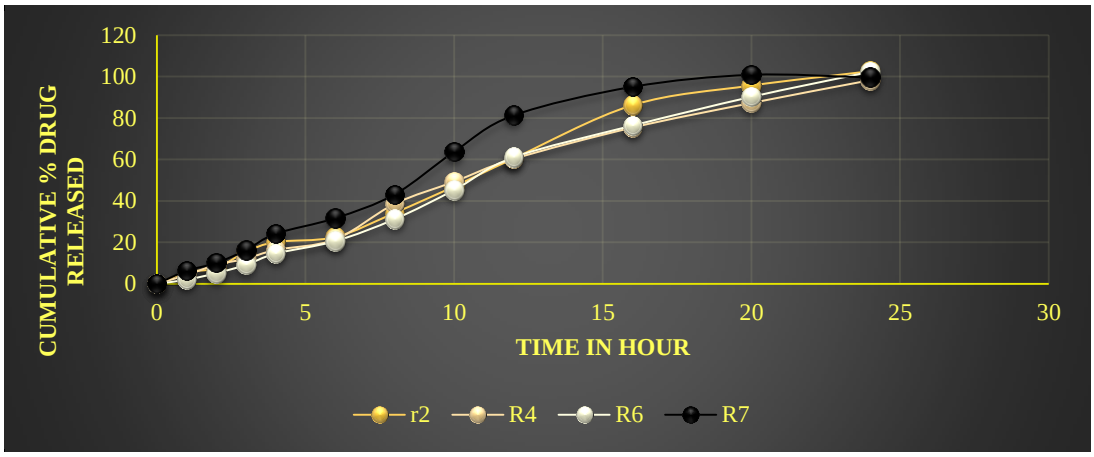

Fig. 2: Dissolution profile comparision of R2, R4, R6 and R7

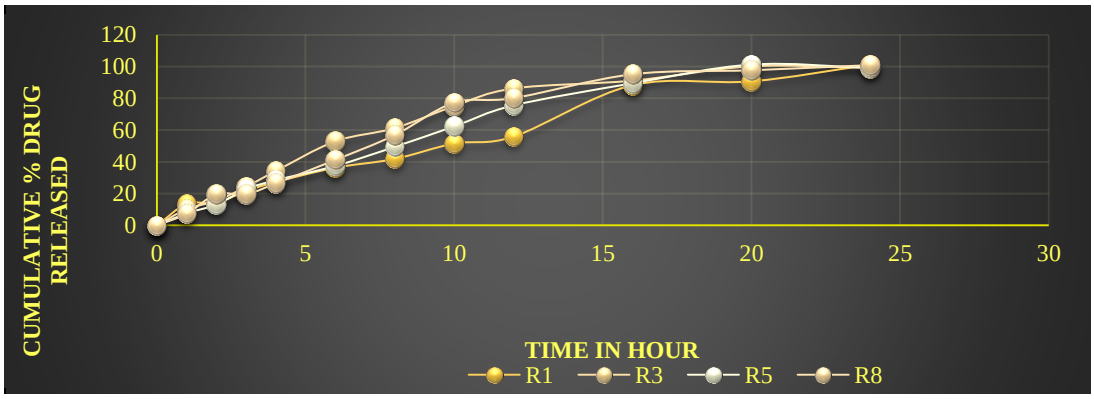

Fig. 3: Dissolution profile comparision of R1, R3, R5 and R8

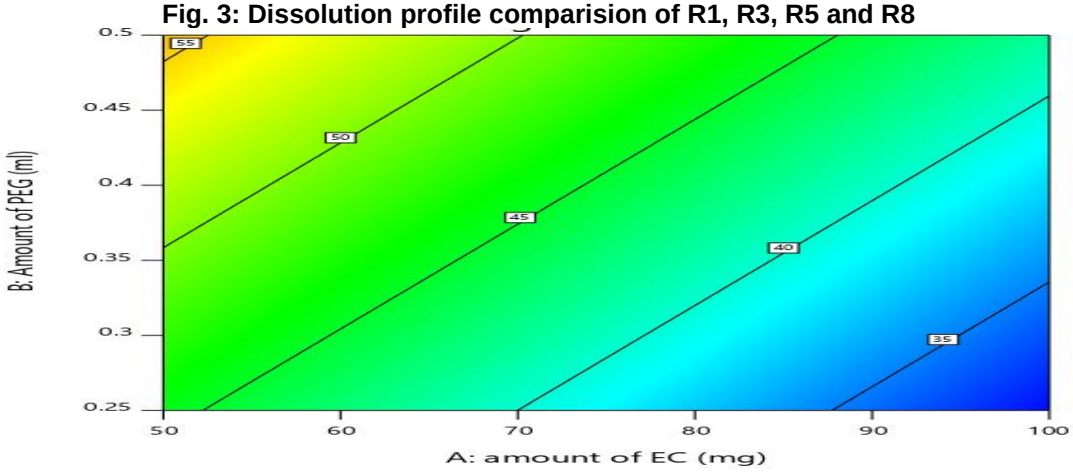

Fig. 4: Contour plot showing drug release at 8th hour from design expert of optimised formulation

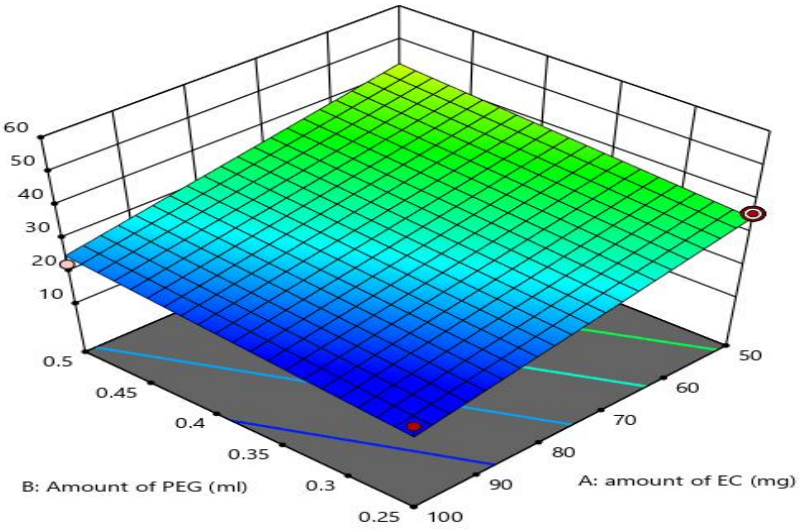

Fig. 5: 3D Response surface methodology graph showing drug release at 8th hour from design expert of optimised formulation

DISCUSSION

1. Weigh variation of Films

Individual weight of 3 films each containing 1 dose of the drug from each formulation was taken and weighed. The films R1 to R8 varies from 0.3415 ± 0.019122 gm to 0.4705 ± 0.012503 gm. This variation is due to the amount of ethyl cellulose used in the formulation, as the drug and other polymers have been kept constant.

2. Thickness of Films

The thickness of the various film formulations were measured using vernier calipers. The average thickness of the films R1 to R8 were found 0.2175 ± 0.007071 mm to 0.28375 ± 0.007071 mm. This variation is due to the amount of ethyl cellulose used in the formulation, as the drug and other polymers have been kept constant.

3. Folding Endurance

Folding endurance of the films R1 to R8 was found to be >150, hence the films were found to be of appropriate strength, due to the presence of PEG as the plasticizer in adequate amount which prevents the breakdown at the folding point as PEG provides flexibility to the films, otherwise the film tends to get brittle.

4. Tensile strength

Tensile strength of the films R1 to R8 was found to be 4.750 ± 0.049 kg/mm^2 to 6.099±0.05 kg/mm^2 as ethyl cellulose and PEG in the formulations give more strength to the film due to the increase in viscosity and elasticity in the formulation.

5. Percent Elongation

Percentage elongation of the films R1 to R8 was found to be 4.750 ± 0.041 to 6.667 ± 0.044. Variation in percentage elongation occurred due to the variation in amount of PEG and concentration of coating solution used in the formulations.

6. Drug content uniformity

The drug content of the films R1 to R8 was found to be 97.45 % to 98.86 %, which was uniform. There is not much deviation in the drug content as the procedure of solvent casting method does not involve any drug losses like other methods of film forming.

7. Surface pH

The surface pH of the films R1 to R8 was found to be 6.7 to 7.2, which is neutral in pH, as the aqueous solution of ethyl cellulose shows neutral pH.

8. Dissolution test

Dissolution testing was performed using the standard paddle apparatus USP type-2 apparatus. The dissolution medium was 900ml of pH 1.2 buffer which simulates the gastric environment relating volume and pH

respectively. The temperature was maintained at 37±0.5℃. Rotating speed was maintained at 50 rpm. Mainly the dissolution behavior has been evaluated by using the design expert software trial version 11, from statistical ANOVA evaluation the dissolution behavior at 2nd hour, shows significant as **P-value is** 0.0376 which is less than 0.0500 and R^2 is 0.8548 adjusted R^2 value 0.7458 and predicted R^2 0.4190 Adequate Precision measures the signal to noise ratio, which was greater than 4 i.e. 6.401 indicates an adequate signal hence the model was applied to navigate the design space. From the coded equation it shows that the factor A is (-3.82) times negative which means the % drug release is inversely proportional to the factor A which is amount of EC present in the formulation so on increasing concentration of ethyl cellulose, the % drug release was decreased at 2nd hour. Ethyl cellulose acts as the sustained release polymer and hydrophobic in nature so the drug enclosed within this polymer could not get easy access to the pH 1.2 buffer which is aqueous in nature. According to Percolation Theory, when a matrix is composed of a water soluble drug and a water insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network.[14] As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse. The total number of ethyl cellulose particles increases when its particle size is reduced. With more ethyl cellulose particles present, the theory predicts that fewer clusters of soluble drug substance are formed. Furthermore, the presence of finite drug clusters (encapsulated drug particles) is more statistically plausible. The resulting pore network becomes less extensive and more tortuous resulting in slower drug release.[15] For the factor B, it is +1.39 times positive which shows increased % drug release values on increasing the amount of PEG as it is hydrophilic plasticizer so in aqueous medium it promotes more solubility of drug from the formulation which happens as the elongation of blended films increased with increasing plasticizer contents, but at high plasticizer contents there was decreases in both tensile strength and modulus which makes the film more accessible for aqueous medium to penetrate the polymer-drug mesh and drug releases more. For factor C, it is -0.1604 times negative on % w/v of EC coating solution which showed decreased % drug release on increasing the concentration of EC coating solution. Coating with Ethyl cellulose acts as the barrier to penetrate the aqueous medium to the formulation and increases the time for the dissolution of drug into the medium. Hence coating with ethyl cellulose decreases the % drug release. Similarly drug release at 6th and 8th hour was found to be significant and release behavior was similar at 2nd hour.

CONCLUSION

Gastro retentive sustained release films in capsules were formulated using HPMC K100M, HPMC K4M, Ethyl cellulose, HPMC 50cps, and PEG as a plasticizer by solvent casting method were found to be good. The drug content was uniform in all the formulations of the films prepared. The low values of standard deviation indicate uniform distribution of drug within the polymer matrices. The drug-polymer ratio was found to influence the release of drug from the formulation. As the polymer level was increased, the drug release rates were found to decrease in a sustained manner. The drug release was also influenced by the concentration of coating solution of the films. As the concentration of coating polymer increased, release of the drug decreased. The results obtained from design expert software version 11 in the form of contour plot, 3D-plot and cuboidal graph clearly shows that increase in the factor A i.e. amount of ethyl cellulose and the factor C decreases the drug release and increase in the factor B increases the drug release. Amount of PEG has influence on release and tensile strength of the sustained release films, drug release increased and tensile strength decreases with increase in amount of PEG as a plasticizer. The mechanism of the drug release for the optimized formulation R2 was found to be Non-Fickian transport with Zero order release. Formulations R1, R4 and R6 showed comparatively less drug release with optimized formulation R2 at 24 hours.

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