

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL FILMS OF RANITIDINE

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ABSTRACT : Bioadhesive formulations have a wide scope of application for both systemic and local effects of drugs. The mucosa is relatively permeable, well supplied with both vascular and lymphatic drainage. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver. The present investigation highlights the formulation and evaluation of mucoadhesive buccal films of ranitidine. The mucoadhesive buccal films of ranitidine were prepared by solvent casting technique using polymers like hydroxy propyl methyl cellulose-15 cps and poly vinyl pyrrolidone. The formulated films were evaluated for their physiochemical parameters like surface pH, percentage moisture absorption, percentage moisture loss, swelling percentage, water vapour transmission rate, thickness, weight of the films, folding endurance and drug content. *In vitro* release studies were performed with pH 6.8 phosphate buffer solution. Good results were obtained both in physico chemical characteristics and *in vitro* studies. The films exhibited controlled release more than 10 h. The *in vitro* release data were fit to different equations and kinetic models to explain release profiles. The kinetic models used were zero order, Higuchi's and Peppas's. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation R5 (2 % HPMC and 1 % PVP). The correlation coefficient value (r) indicates the kinetic of drug release was zero order. The formulation was found to be right and suitable candidate for the formulation of ranitidine buccal film for therapeutic use.

Key words: Ranitidine, buccal films, solvent casting technique, *in vitro* release studies, zero order

INTRODUCTION

The buccal region offers an attractive route for systemic drug delivery for extended periods of time. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. Over the last two decades mucoadhesion becomes of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (with in gastro intestinal tract) or systemic delivery, by retaining a formulation in intimate contact with absorption site (in the buccal cavity). Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time¹. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver². These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. Buccal film may be preferred

over adhesive tablet in terms of flexibility and comfort. In addition they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively³.

Ranitidine is a competitive inhibitor of histamine H₂-receptors, drug of choice in the treatment of ulcer and Zollinger Ellison syndrome and readily absorbed from gastro intestinal tract⁴. The bioavailability of ranitidine following oral administration is about 50 % which might be due to colonic degradation by colonic bacteria⁵. The bioavailability of ranitidine is markedly lower from the human colon than the upper part of gastro intestinal tract. Various attempts have been made to develop the formulation of mucoadhesive buccal films of ranitidine for improving and enhancing bioavailability in a controlled release fashion. It may also be possible to

avoid the first pass effect and presystemic elimination in the gastro intestinal tract and liver.

The present investigation highlights the formulation and evaluation of mucoadhesive buccal films of ranitidine. The mucoadhesive buccal films of ranitidine were prepared by solvent casting technique using polymers of hydroxy propyl methyl cellulose-15 cps and poly vinyl pyrrolidone.

MATERIALS AND METHODS

Ranitidine, Hydroxy propyl methyl cellulose-15 cps, Poly vinyl pyrrolidone was procured from Drugs India, Hyderabad, India. Ethanol (O.R Distilleries, Renigunta, India), Dichloromethane (Universal laboratories pvt ltd, Mumbai, India), Propylene glycol (Karnataka fine chem. industries, Bangalore, India). All other chemicals were of analytical grade and procured from S.D fine chemicals, Mumbai, India. The films were prepared by solvent casting method. Concentrations of ranitidine were measured with UV-VIS Spectrometer Labomed, Inc, USA. (Model No: 2602).

Fabrication of Ranitidine Buccal Films

The films were prepared by the method of solvent casting technique⁶⁻⁸ employing 'O' shape ring placed on a glass surface as substrate. Composition of a single circular cast film of various formulations is given in the Table.1.

The calculated quantities of polymers Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC) and Poly Vinyl Pyrrolidone (PVP) were dispersed in ethanol and dichloromethane. An accurately weighed 100 mg Ranitidine was incorporated in polymeric solutions after levigation with 30 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. Then this were casted on a glass surface employing 'O' shape ring having 4.2 cm in diameter is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried films were separated and the backing membrane used was aluminium foil. Then the formulations were stored in a desiccator until further use.

Surface pH of films

Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2 % (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then pouring the solution into a petridish till gelling at room temperature. The surface pH⁹ was measured by means of a pH paper placed on the surface of the swollen patch. The mean of three reading was recorded.

Percentage moisture absorption (PMA)

The percentage moisture absorption¹⁰ test was carried out to check the physical stability of the buccal films at high

humid conditions. In the present study the moisture absorption capacity of the films were determined as follows. Three 1cm diameter films were cut out and weighed accurately then the films were placed in desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccator at 79.5 %. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found.

Percentage moisture absorption =

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss (PML)

Percentage moisture loss¹⁰ was also carried to check the integrity of films at dry condition. Three 1cm diameter films was cut out and weighed accurately and kept in desiccator's containing fused anhydrous calcium chloride. After 72 hours the films were removed, weighed. Average percentage moisture loss of three films was found out.

Percentage moisture loss =

$$\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Swelling Percentage (% S)

A drug loaded films were placed in a thoroughly cleaned petridish and a graph paper was placed beneath the petridish, to measure the increase in area due to swelling of the film. Fifty ml of pH 6.8 phosphate buffer was poured into the petridish. An increase in the weight of the patch was noted in 15 min intervals for 60 min and the weight was calculated. The swelling percentage^{11,12} was calculated by using the following formula,

$$\% S = \frac{X_t - X_0}{X_0} \times 100$$

Where, % S - swelling percentage, X_t - the weight of swollen film after time t, X_0 -weight of film at zero time zero.

Water vapour transmission rate (WVT)

For water vapour transmission rate¹³ study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of calcium chloride was taken in the cell and the polymeric films measuring 2 cm² area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccators containing saturated solution of potassium chloride. The humidity inside the desiccators was found in between 80 – 90 % RH. The cells were taken out and weighed after 18, 36, 54 and 72 hrs. From increase in weights the amount of water vapour transmitted and the rate at which water vapour transmitted were calculated by using the following formula.

$$WVT = WL/S$$

Where, W is water vapour transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm².

Film weight and thickness

For evaluation of film weight three films of every formulation were taken and weighed individually on a digital balance (ESSAE, Goa, DS-852J). The average weights were calculated, similarly, three films of each formulation were taken and the films thickness was measured using Digital vernier caliper (Absolute Digimate) at six different places and the mean value was calculated.

Folding endurance

Folding endurance¹⁴ of the film was determined by repeatedly folding one patch at the same place till it broke or folded manually, which was considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done for three films.

Drug content uniformity

A film was cut into three peaces of equal diameter were taken in separate 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, suitably diluted and analyzed at 313 nm in a UV Spectro meter. The average of drug content of three films was taken as final reading.

In vitro release study

The drug release studies were performed with USP dissolution test apparatus⁸. (Paddle method). The USP dissolution apparatus was thermostated at the temperature of 37±1° C and stirred at rate of 50 rpm. Each film was fixed on a glass slide with the help of cyanoacrylate

adhesive so that the drug could be release only from upper face. Then the slide has immersed in the vessel containing 500 ml of pH 6.8 phosphate buffer solution. The aliquots of 1 ml were withdrawn at the time interval of every hour and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study. The samples were analyzed at 313 nm in a UV-VIS Spectrometer and cumulative amount of drug release at various time intervals was calculated.

RESULTS AND DISCUSSION

Buccal films of Ranitidine were prepared by the method of solvent casting technique employing 'O' shape ring having diameter of 4.2 cm placed on a glass surface as substrate with mucoadhesive polymers of HPMC 15 cps and PVP. Ethanol and Dichloromethane is used as the solvents. Propylene glycol was used as the plasticizer as well as penetration enhancer. The drug delivery system was formulated as a matrix controlled drug delivery. The prepared ranitidine buccal films were evaluated or characterized based upon their physico chemical characteristics like surface pH, PMA, PML, swelling percentage, WVT, thickness, weight, folding endurance and drug content. These results were shown in Table.2. The *in vitro* drug release studies were performed by using USP dissolution apparatus (paddle method) was thermostated at 37±1°c. i.e. the films were fixed with the help of cyanoacrylate adhesive so that the drug released only from upper face.

Considering the fact that acidic or alkaline pH may affect or cause the irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the films were determined by using suitable means. The all prepared formulation of ranitidine buccal film showing the pH range with in the range of salivary pH i.e. 6.5 to 6.8. The observed surface pH of the formulation R1, R2, R3, R4 and R5 are 6.56±0.152, 6.66±0.152, 6.63±0.115, 6.60±0.173 and 6.56±0.115 respectively. The results are found that there is no significant difference of surface pH in all the formulation. Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML. The observed results of PMA and PML were shown in the tabular column. The observed PMA was in order of R5>R2>R4>R3>R1. Amongst all the formulation the high value of PMA can be observed in R5 and R2 this is due to the increasing swelling behavior of HPMC and the PML was found in the order of R1>R2>R5>R4>R3 i.e. 1.42±0.01>1.24±0.01>1.16±0.02>1.06±0.02>0.96±0.41 due to the high degree of hydration of mucoadhesive polymer like HPMC. So the formulation having only HPMC shows high PML than the formulation having HPMC and PVP.

The drug loaded films were showing more swelling percentage than the drug free film this is due to increase water up take of the drug. The swelling percentage of the formulated buccal films was observed in pH6.8 phosphate buffer. The more swelling was pronounced in

formulation R5 and R2 which contain combination of HPMC 2 % and PVP 1 % and HPMC 2 % alone respectively. The observed swelling percentage was in order of $R5 > R2 > R4 > R3 > R1$

i.e. $131.23 \pm 3.35 > 96.63 \pm 0.55 >$

$87.98 \pm 1.02 > 78.24 \pm 1.37 > 69.9 \pm 0.85$.

Water vapour transmission studies indicated that all the films were permeable to water vapour. The water vapour transmissions were more in the case of formulation R5. The water vapour transmission was found in the order of $R5 > R4 > R2 > R3 > R1$.

The film thicknesses were observed by using digital vernier caliper and found to be in the range of 0.103 ± 0.013 mm to 0.216 ± 0.036 mm and weight of the films was found to be in the range of 212.33 ± 2.081 mg to 418.33 ± 1.527 mg.

The folding endurance was measured manually, by folding the film repeatedly at a point till they broke. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. Hence the breaking time was taken at the end point. The folding endurance was found to be highest for formulation R5 (328 ± 2.645) and the lowest for formulation R1 (186 ± 7.211). It was found that the folding endurance was increased with the addition of PVP with HPMC and increase in the percentage of HPMC (R2, 301.33 ± 3.511).

The observed results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 98 ± 1 to 99.96 ± 0.057 . In case of film R1, the percent recovery was relatively low may be due to less percentage of HPMC.

In vitro drug release studies were performed for all the prepared formulation by using phosphate buffer pH 6.8 as dissolution medium and measuring drug concentration UV spectrophotometrically at 313 nm. The studies were performed upto 10 to 12 h. The results of *in vitro* studies are shown in the Table. 3. Distinguishable difference was observed in the release of Ranitidine containing HPMC and PVP. The graph was plotted by taking Cumulative percentage release Vs Time and the graphs were shown in the Fig. 1. The cumulative percentage drug release was observed in the formulation R1 after 10 h was found to be 97.56 %. The cumulative percentage drug release was observed in the formulation R2 and R3 after 11 h was found to be 98.08 % and 92.16 % respectively. The cumulative percentage drug release was observed in the formulation R4 and R5 after 12 h was found to be 92.25 % and 90.76 % respectively. The observed results were indicating the highest percentage of HPMC showing good release characteristics in the formulation R2 due to

hydration and excessive swelling percentage of polymer. But in the presence of PVP may retard the release of drug more than 11 to 12 h may be due to increase in bioadhesion property of polymer. So out of all the formulation R5 is retard the release rate and used to achieve the controlled release characteristics more than 12 h than the other formulations.

The obtained results in these formulations were plotted in various model treatment are as follows. i.e. Cumulative percentage release of drug Vs Square root of time (Higuchi's) and Log cumulative percentage release Vs Log time (Peppas). The formulations R1, R2, R3, R4 and R5 comparative plotted graphs of Higuchi's and Peppas were shown in the Fig. 2 and 3 respectively.

To find out the mechanism of drug release¹⁵ from hydrophilic matrices, the *invitro* dissolution data of each formulation with different kinetic drug release equations. Namely Zero order: $Q = K_0 t$; Higuchi's square rate at time: $Q = K_H t^{1/2}$ and Peppas: $F = K_m t^n$, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K_0 is zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporating geometric and structural characteristic of the films and n is the diffusion exponent indicative of the release mechanism. The correlation coefficient values (R) indicate the kinetic of drug release was zero order and the mechanism of drug release was by peppas model indicates the super case II transport evidenced with diffusion exponent values (n) Table. 3.

CONCLUSION

The Ranitidine buccal films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate, using polymers of Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC) and Poly Vinyl Pyrrolidone (PVP) were dispersed in ethanol and dichloromethane and 30 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The prepared ranitidine buccal films were evaluated or characterized based upon their physico chemical characteristics like surface pH, PMA, PML, swelling percentage, WVT, thickness, weight, folding endurance and drug content. The *in vitro* release studies were performed. Good results were obtained both in physico chemical characteristics and *in vitro* studies. Hence the formulations of Ranitidine bioadhesive buccal film promising one as the controlled drug delivery, improve bioavailability and the dose of ranitidine could be minimized and hence prevent the colonic degradation of ranitidine by colonic bacteria.

TABLE: 1: THE COMPOSITION OF PATCHES PREPARED USING RANITIDINE

| Batch code | Drug in mg | Polymer in % | | Solvents in ml | | |
|------------|------------|--------------|-----|----------------|------------------|---------------------------|
| | | HPMC | PVP | Ethanol | Dichloro methane | Propylene glycol 30 % w/w |
| R1 | 100 | 1 | -- | 3.5 | 6 | 0.5 |
| R2 | 100 | 2 | -- | 3.5 | 6 | 0.5 |
| R3 | 100 | 1 | 1 | 3.5 | 6 | 0.5 |
| R4 | 100 | 1.5 | 1 | 3.5 | 6 | 0.5 |
| R5 | 100 | 2 | 1 | 3.5 | 6 | 0.5 |

TABLE: 2: PHYSIOCHEMICAL EVALUATION OF BUCCAL FILMS OF RANITIDINE

| Formulation code | Surface pH \pm S.D | PMA \pm S.D | PML \pm S.D | Swelling Percentage \pm S.D | Water Vapour Transmission rate (mg/cm ² /hr) \pm S.D | Thickness in mm \pm S.D | Weight of films in mg \pm S.D | Folding endurance \pm S.D | Drug content in mg \pm S.D |
|------------------|----------------------|------------------|-----------------|-------------------------------|---|---------------------------|---------------------------------|-----------------------------|------------------------------|
| R1 | 6.56 \pm 0.152 | 2.84 \pm 0.015 | 1.42 \pm 0.01 | 69.90 \pm 0.85 | 6.02 \pm 0.141 | 0.103 \pm 0.013 | 212.33 \pm 2.08 | 186.0 \pm 7.211 | 98.0 \pm 1.0 |
| R2 | 6.66 \pm 0.152 | 3.88 \pm 0.115 | 1.24 \pm 0.01 | 69.6 \pm 0.55 | 12.66 \pm 0.155 | 0.183 \pm 0.007 | 318.33 \pm 1.52 | 301.3 \pm 3.511 | 99.92 \pm 0.11 |
| R3 | 6.63 \pm 0.115 | 2.93 \pm 0.092 | 0.96 \pm 0.41 | 78.24 \pm 1.37 | 10.54 \pm 0.361 | 0.168 \pm 0.014 | 317.66 \pm 3.05 | 293.3 \pm 4.509 | 99.16 \pm 0.291 |
| R4 | 6.60 \pm 0.173 | 2.95 \pm 0.070 | 1.06 \pm 0.02 | 87.96 \pm 1.02 | 14.08 \pm 0.236 | 0.205 \pm 0.008 | 369.86 \pm 1.52 | 289.6 \pm 3.055 | 99.50 \pm 0.50 |
| R5 | 6.56 \pm 0.115 | 4.07 \pm 0.075 | 1.16 \pm 0.02 | 131.23 \pm 3.35 | 17.06 \pm 0.196 | 0.216 \pm 0.036 | 418.90 \pm 1.52 | 328.0 \pm 2.645 | 99.96 \pm 0.057 |

TABLE: 3: DIFFUSION CHARACTERISTICS OF RANITIDINE BUCCAL FILM FORMULATIONS

| FORMULATION CODE | CORRELATION COEFFICIENT VALUES | | DIFFUSION EXPONENT VALUE (n) |
|---------------------|--------------------------------|--------------|---------------------------------|
| | (R) | | |
| | Zero Order | Peppas Model | |
| R1 | 0.99136 | 0.99436 | 1.22242 |
| R2 | 0.99142 | 0.99807 | 1.25457 |
| R3 | 0.99014 | 0.99658 | 1.25369 |
| R4 | 0.99415 | 0.99565 | 1.26906 |
| R5 | 0.99360 | 0.99850 | 1.36389 |

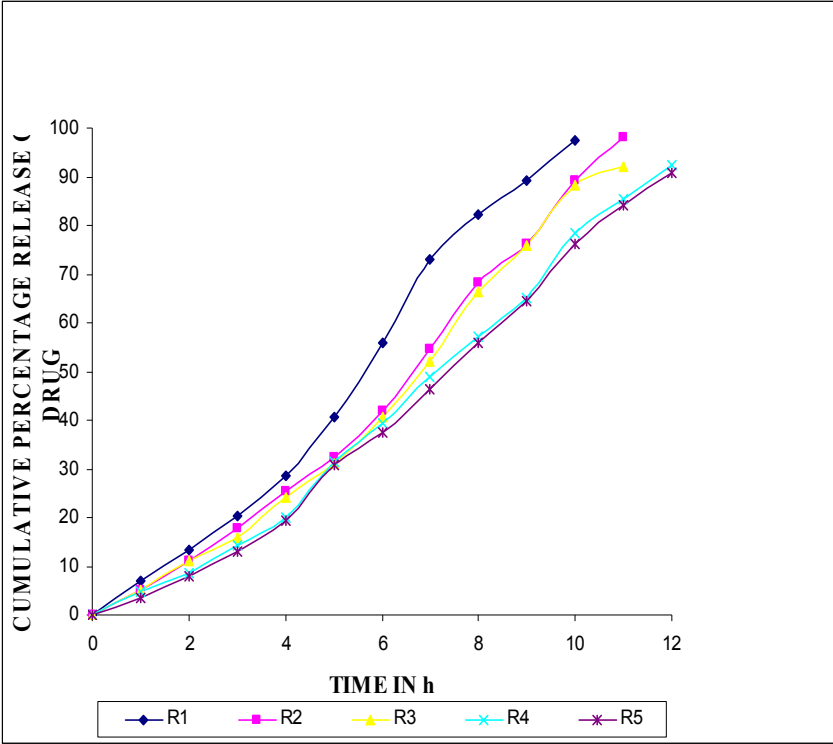


Fig. 1: *In vitro* drug release profiles of formulation R1, R2, R3, R4 and R5

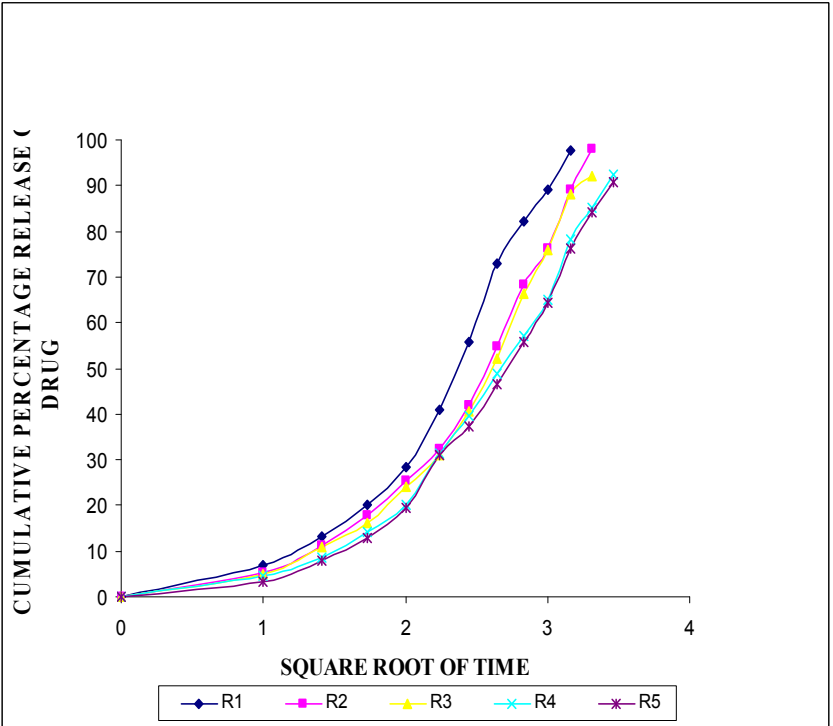


Fig. 2: Higuchi's plot for formulation R1, R2, R3, R4 and R5

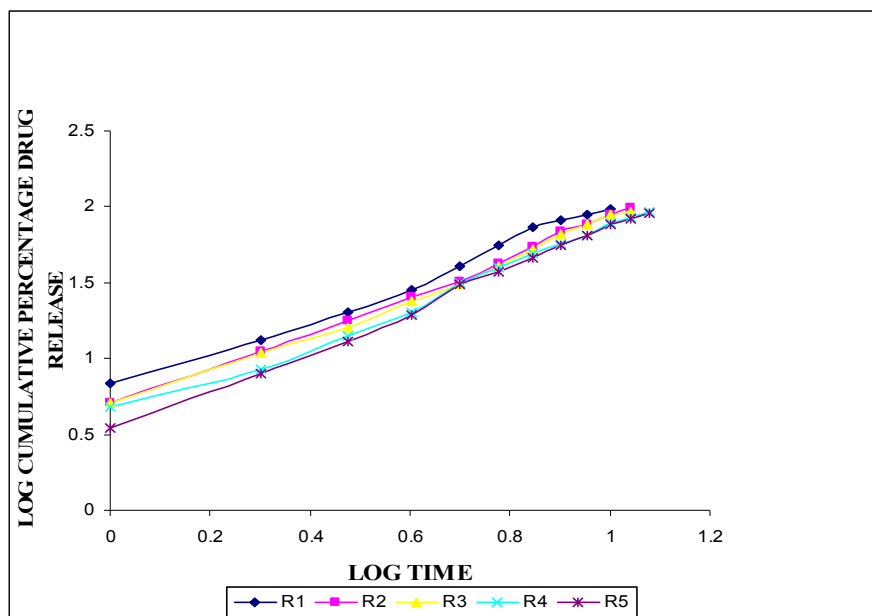


Fig. 3: Peppas plot for formulation R1, R2, R3, R4 and R5

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