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Development and Evaluation of Gastroretentive Drug Delivery System for Theopylline using Psyllium Husk

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ABSTRACT: Sustained release gastroretentive drug delivery systems (SRGRDDS) enable prolonged & continuous input of the drug to the upper parts of the gastrointestinal tract (G.I.T) and improve the bioavailability of medications that are characterized by narrow therapeutics window. The aim of this project was to develop one daily SR floating matrix tablet for theophylline using psyllium husk as release controlling polymer and to compare the release pattern with synthetic polymer i.e. HPMC K100 M. Other polymers like HPMC K15 M, sodium bicarbonate, Ac-Di-Sol etc. were also used. Formulations were prepared by wet granulation method and evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content, and *in vitro* release profile. It was found that Floating duration of the formulation containing psyllium husk alone was less than that containing similar concentration of HPMC K100M. The floating duration was made comparable with the formulation containing similar amount of HPMC K100M by addition of HPMC K15M. Release rate of the formulation containing psyllium husk in combination with HPMC K15M more than the formulation containing similar amount of HPMC K100M. It was found that dimensional stability increased with psyllium husk concentration while floating lag time decreased. The *in vitro* release data and drug release mechanism of the optimized formulation followed the Higuchi kinetics and nonfickain type respectively. It can be concluded that Psyllium husk can be a promising polymer for gastroretentive floating drug delivery systems in combination with synthetic polymers.
Keywords: Theophylline, Floating matrix, Gastroretentive, Sustained release, Psyllium husk

INTRODUCTION

Oral controlled release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems [1]. An Ideal drug delivery system should posses two main properties: (1) It should be a single dose for the whole duration of the treatment. (2) It should deliver the active drug directly at the site of action [2]. One novel approach in this area is gastroretentive drug delivery system (GRDDS). Prolonging the gastric retention of the delivery system is some time desirable for achieving therapeutics benefits of drug that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in or are degraded by the alkaline pH or they encounter at the lower part of the GIT. GRDDS are thus beneficial for such drugs by improving their bioavailability, therapeutics efficacy and possible reduction of the dose. Apart of these advantages, these systems offer various pharmacokinetics advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels [3].

Gastrointestinal retention depends on many factors such as density of the dosage forms, fasting and fed condition, nature of the meal taking, sleep, posture etc [4]. It also depends strongly on a complicated and unpredictable gastric emptying with migrating myoelectric complex motility of stomach. Several techniques including floating i.e. Effervescent Systems

and non effervescent Systems, swelling or expendable, inflation and adhesion etc have been explored to increase the gastroretention of dosage forms. The above mention approaches for gastrointestinal retention work by one or more of these mechanisms [5, 6, 7 8].

The objective of this study was to prepare a sustained release floating drug delivery of theophylline using psyllium husk as rate controlling polymer and compare with formulation prepared with HPMC k 100 M.

Native of psyllium husk was used as a release controlling polymer in the present investigation because of regulatory acceptances. Psyllium husk possesses good swelling and gelling properties and therefore, when used as a matrix forming agent in the modified release formulation, it forms a swollen gel by the time thus it is able to controlled drug release [9, 10, 11].

Adjutants of natural sources like Psyllium husk are preferred over synthetics material due to their nontoxicity, low cost, ease of availability, high affinity of water (swelling index is about 20 times in volume, chemically inert & purely mechanical action in the alimentary canal body does not assimilate it.[12,13]

Theophylline was used as a model drug for this work. Theophylline is a widely used bronchodilator with the moderate aqueous solubility and narrow therapeutic index. The therapeutic effects are correlated with its plasma concentration over a narrow range of 10 to 15 µg/ml and side effects are related to higher plasma concentration. These features made theophylline a popular drug to formulate in to sustained release dosage form. Theophylline is mainly absorbed in the upper part of small intestine. So retention of the drug in the stomach will be beneficial to improve the absorption of the drug [14, 15, 16].

MATERIALS AND METHODS

Theophylline (Aurochem Pvt, Thane), Psyllium Husk (Atlas Ind. Sidhpur, Gujrat), HPMC (Clorcon, Goa), NaHCO3 (CDH Labs, Delhi), Sodium CMC (CDH Labs,Delhi), Mg-stearate (CDH Labs,Delhi) etc. All these chemicals were analytical grades.

Fabrication of Floating Matrix Tablet

Different batches of floating matrix tablets were prepared by wet granulation method using different ratio of drug and psyllium husk or HPMC K 100 M. The respective powders (drug & polymers) were blended thoroughly and a dump mass was prepared by adding the granulating agent (5 % PVP K-30 in isopropyl alcohol). Dump mass was passed through sieve number 22 and dried in hot air oven at 60^0C for one hour. After drying, granules were further passed through sieve number 20 to attain the uniformity in granules. Finally, optional additives like magnesium stearate and talc were added after evaluating the flow properties of dried granules and blended in a mortar and pestle.

The required amount of the blend was weighed and fed manually into the die of single punch tabletting machine (HICON Single station punching machine, India) to produce tablets using concave faced punch of suitable diameter. The tablet hardness was maintained in the range of 2-5 kg/cm^2. **[Table 1]**

Floating Capacity

The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900 ml of simulated gastric fluid. The time interval between introduction of the tablet in to the dissolution medium and its buoyancy to the top of the dissolution medium was taken as buoyancy lag time and time for which the tablet constantly floats on the surface of the medium (duration of buoyancy) was observed visually.**Table 1]**

Dimensional Stability

The dimensional stability of formulation was studied using USP Dissolution Apparatus II in 900 ml simulated gastric fluid. The dimensional stability of the theophylline floating tablets was observed visually. **[Table 1]**

Determination of Swelling Index

The swelling index of the tablets was studied using the USP dissolution apparatus II in 900 ml of simulated gastric fluid. The temperature was maintained at 37±0.5^{0}C and rotation speed 50 rpm. The swollen weight of the tablets was determined at a predefined time intervals. The tablets were blotted with tissue paper to remove the excess medium and reweighed. The swelling index was calculated by the following formula:

Swelling index = (Wt – Wo / Wo) × 100

Where: Wo is the initial weight of matrix tablet.

Wt is the weight of swelling matrix tablet after t times.

Erosion Studies

The preweighed tablets were placed in USP dissolution apparatus II in 900 ml of simulated gastric fluid and subjected to dissolution. The temperature was maintained at 37±0.5^{0}C and rotation speed 50 rpm. The tablets were removed after 12 hours from the dissolution vessels and dried to constant weight in hot air oven at 50^{0}C-60^{0}C. The percentage matrix eroded was calculated by using following formula:

Percentage Matrix Eroded =

(Wt of polymer eroded / Wt of initial Matrix)×100

Weight of polymer eroded = (Total weight loss – Amount of drug released)

***In-Vitro* Release Study**

The release of theophylline from the tablets was studied using the USP dissolution apparatus I in 900ml simulated gastric fluid of pH 1.2. The temperature was maintained at 37 ± 0.5^{0}C. The rotation speed was 75 rpm. Five ml of aliquot was withdrawn at a predetermine intervals, and medium was replenished with five ml of fresh medium at each time interval. The drug solution was filtered. Aliquot of filtrate was diluted suitably and analyzed spectrophotometrically (Shimadzu 1700, Japan) at 270 nm. The percentage of drug released at each time interval was determined. **[Table 1]**

RESULTS AND DISCUSSION

Floating Capacity

The fasted state is associated with various cyclic movement commonly referred as **migrating motor complex** (MMC). The third phase of MMC (burst phase) is characterized by the large, intense and regular contraction termed as housekeeper waves that swept out the particulate matter (undigested food particles) from the stomach and lasts to 10 to 20 minutes. To prevent the formulation from the effect of this phase, tablet should be float as fast as possible after reaching in the stomach.

In similar way floating duration & dimensional stability are important in case of once daily formulation to obtain the continuous and constant drug release up to the 24 hrs. If physical integrity of the formulation is not maintained, the tablet could break down in to the small fragments and escape from the upper part of GIT.

The floating lag time and duration of floating of formulation P1 containing 200 mg of psyllium husk was 15 minutes & 5 hrs respectively. This formulation was not able to maintain the dimensional stability up to 24 hours. As the concentration of the psyllium husk increased from 200 to 400 (1: 2, drug: polymer ratio), the floating lag time reduced to 12 minutes and duration of floating was 8 hrs. The dimensional stability was maintained up to 24 hrs (batch P3).

Incorporation of HPMC K15M enhanced the floating duration (batch P5= 24 hrs). This might be due the synthetics nature of HPMC K15M, which hydrated at a faster rate than that of psyllium husk. HPMC K15M also helps to maintained dimensional stability at initial stage. There was no measurable effect of HPMC K15M on FLT. Formulation prepared with HPMC K100M in similar amount as that of psyllium and HPMC K15M combination (batch P5) showed the floating duration 24 hrs.

Incorporation of sodium bicarbonate reduced FLT in both psyllium and HPMC K100M formulations (batch P7 = 1 minutes, P11 =1.5 minutes). As the concentration of sodium bicarbonate increased the floating lag time decreased (batch P8 = 0 minutes, P12 =0 minutes). This might be due to generation of CO_2 by addition of sodium bicarbonate which gets entrapped in the gel layer and helps to tablets become buoyant in less time.

As the hardness increased, the floating lag time also increased. On immersion of tablet of hardness around 2-kg/ cm^2 in dissolution medium, the tablet floated immediately (batch P15 =0, batch P17= 0) as compared to the formulation of 4 kg/ cm^2 hardness which take more time (data is not showed) to come up to the surface of dissolution medium. The tablets hardness 6 kg /cm^2 showed no floating. In fact, buoyancy of the tablet is governed by both the swelling the outer surface of the tablets when it comes in the contact with the gastric fluids and the presence of the internal void (Porosity) in the dry centre of the tablet. These two factors are essential for the tablet to acquire bulk density less than that of the gastric fluid i.e. 1.04 gm/cm^3 that helps it to remain buoyant on gastric fluids. Compression force of these tablets to high degree hardness may result in reduction of porosity of the tablet and moreover, the compressed hydrocolloids particle on the surface of the tablet fail to hydrate rapidly when the it come in to contact with the gastric fluid and as a result, the capability of the tablets to float is significantly reduced.

Swelling Index

Swelling is a vital factor to ensure floating. To obtain floating, the balance between the swelling and water must be reported. The formulation containing psyllium husk took about 6 to 8 hrs to complete swell as compared to the formulation prepared with HPMC K100 M that took 4-5 hrs to complete swell. In the first hour of study, the swelling index for formulation prepared with psyllium husk alone was 57.1% (batch P3) and 85.92 % (batch P10) for the formulation prepared with HPMC K 100 M. The swelling index after complete swelling was 310.87% for formulation prepared with psyllium alone (batch P3) and 304.32 % for formulation prepared with HPMC K 100M alone (batch = P10). The difference in the swelling index was because of the psyllium husk is a natural agent took more time to hydrate as compared to synthetic agent HPMC K 100 M. Addition of HPMC K 15 M in formulation containing payllium enhanced the swelling index at initial stage (batch P4= 67.9 %) but swelling index after complete swelling was decreased (batch P4= 305.87%) [Figure 1A]. Addition of Ac- Di –Sol in bath cases increased swelling index. This might be due to the grater efficiency Ac- Di –Sol for water. Finally the swelling index optimized formulation after complete swelling was for 305.25 % formulation containing psyllium in combination with HPMC K 15

M (batch P15) and 315.59% formulation containing HPMC K 100 M (batch P17) [Figure 1B & Figure 1C].

Erosion Study

The percentage of matrix eroded was more for the formulations prepared with psyllium husk alone (batch P3 = 7.49%) than that of HPMC K100M (batch P10=2.28%) after 12 hours study. Addition of HPMC K15M in formulation containing psyllium husk reduced the erosion (batch P4=5.87 %). As the concentration of HPMC K15M increased, the amount of matrix eroded decreased (batch P 6= 4.87 %). There was no measurable effect of sodium bicarbonate and Ac-Di-Sol on erosion.

***In-vitro* Release Study**

Two different polymers were used to prepare the floating matrix tablets. It was observed that type of polymer influences the release pattern. The formulations prepared with psyllium husk alone showed the more sustained release (batch P3 =57.89 %) than those prepared with HPMC K 100M (batch P10 = 62.15%) after 24 hrs study. But formulations prepared with psyllium husk alone were not able to Float up to 24 hrs. To enhance floating duration HPMC K 15M was added. The formulations containing 100 mg HPMC K15M with 300 mg psyllium able to float up to 24 hrs but the release rate was enhanced (batch P5= 62.35 %). As the amount of HPMC K 15M increased, the percentage of drug release increased (batch P6 = 65.53%). (Figure 2 A)

Sodium bicarbonate showed the opposite effect on percentage drug release. This might be due to the alkaline nature of the sodium bicarbonate, which create an alkaline environment around the tablet. Theophylline was less soluble in the alkaline environment that decreased the release of drug from the formulation. Formulation containing 10 % NaHCO3 shown the grater drug release after 24 hrs (batch P7= 61.42%, P11= 60.34%) as compared to formulation 20 % NaHCO3 (batch P9 = 57.77%, batch P13 = 54.33%). (Figure 2 B & Figure 3 A)

In order to improve the release profile of formulation prepared with psyllum husk as well as HPMC K100 M, the Ac-di-Sol was used. Formulation containing 0 % of Ac-Di-Sol showed the % drug release 60.47 % (batch P8 & 57.63% (batch P12). Formulation containing 5% Ac-Di-Sol showed the cumulative % drug release was 70.27 % (batch P14) and 65.31 %(batch P16). Formulation containing 10% Ac-Di-Sol showed the % drug release was 87.25% (batch P15) and (batch P17) 83.21%. The reason behind it Ac-Di-Sol is a super disintegrate and creates pores in the gel network prepared by these polymers and improve thee release of the drug increase. (Figure 2 C & Figure 3B)

Finally, the cumulative percent release from optimized formulation prepared with psyllium in combination with HPMC K15M(batch P15 = 87.25%) was more (batch P15 = 87.25%) than that of formulation prepared with HPMC K100M (batch P17= 83.21%).Figure 4

RELEASE KINETICS

The *In-vitro* release data of optimized formulations were treated with different kinetics models to explain the release kinetics of theophylline from floating matrix tablets. These models were zero order, first order, higuchi model, hixon-crowel model and korsemayer peppas model. Higuchi model was considered as the best fitted model with the highest value of correlation coefficient (r^2 =0.997). The release data were further treated by Ritger-Peppas or power law to calculate the value of n (release exponent). The values of n (release exponent) for optimized formulations were found to be 0.5422 for batch P15 (prepared with psyllium hush in combination with HPMC K 15 M) and 0.6448 for P17 (prepared with HPMC K 100 M). The value of n indicates that the release mechanism from optimized formulation was the non-fickian diffusion (anomalous type), controlled by the diffusion through swollen matrix.

STATISTICAL ANALYSIS

Analysis of variance (ANOVA) was applied to identify the significance difference in percent drug release of various formulations prepared by psylluim husk and HPMC K 100 M. ANOVA interpretation showed that there was no significance difference in cumulative percent drug release of formulation prepared with psyllium husk and HPMC K 100M at 5 % level of significance ($\alpha = 0.05$).

STABILITY STUDIES

The optimized formulation was subjected to stability studies at a room temperature and 40^0C / 75% RH. These formulations were evaluated for their appearance, possible weight gain in drug content and in-vitro release study. Negligible changes were seen in different physicochemical parameters at a room temperature as well as 40^0C/ 75 % RH. There was no significance difference in in-vitro release and in content uniformity after three-month stability study at both room temperature and accelerated conditions.

CONCLUSION

Thus from the whole research work it can be concluded that the objective of the proposed project has been fulfilled and GRDDS for theophylline using psyllium husk and HPMC K 100M have been successfully formulated and evaluated. The conclusion of the studies can be summarized as:

Psyllium husk might be a promising polymer for gastroretentive floating drug delivery systems in combination with synthetic polymer like HPMC K 15M. Use of HPMC K 15M with psyllium husk

enhanced the floating duration and help to maintain the dimensional stability at initial stage, which is necessary in case of once daily formulations. Ac-di-Sol used to improve the release profile. ANOVA study showed that formulation prepared with psyllium husk containing HPMC K 15 M showed the comparable drug release as that of HPMC K 100 M. Optimized formulation followed the Higuchi kinetics while the drug release mechanism was found to be anomalous types or nonfickain type & controlled by diffusion through the swollen matrix. Optimized formulation was found to be stable at all stability conditions.

Table 1

F.C.	Amount (mg)				Amount (%)			FLT (min)	FD (hrs)	DS (hrs)	Drug released (24 hrs)
	Drug	P	HPMC 15M	HPMC 100M	Ac-di-Sol	$NaHCO_3$	PVP				
P1	200	200	-	-	-	-	5	15	5	12	-
P2	200	300	-	-	-	-	5	13	8	17	-
P3	200	400	-	-	-	-	5	12	8	24	57.89±1.3
P4	200	350	50	-	-	-	5	10	15	24	58.29±0.36
P5	200	300	100	-	-	-	5	9	24	24	62.35±0.89
P6	200	250	150		-	-	5	12	24	24	65.53±0.85
P7	200	300	100	-	-	10	5	1	24	24	61.42±1.41
P8	200	300	100		-	15	5	0	24	24	60.47±1.69
P9	200	300	100		-	20	5	0	20	24	57.77±0.87
P10	200	-		400	-	-	5	10	24	24	62.15±0.92
P11	200	-	-	400	-	10	5	1.5	24	24	60.34±0.23
P12	200	-	-	400	-	15	5	0	24	24	57.63±1.62
P13	200	-	-	400	-	20	5	0	24	24	54.33±0.53
P14	200	300	100	-	5	15	5	0	24	24	70.27±2.1
P15	200	300	100	-	10	15	5	0	24	24	87.25±1.12
P16	200	-	-	400	5	15	5	0	24	24	65.31±1.87
P17	200	-	-	400	10	15	5	0	24	24	84.21±0.69

F.C. = Formulation Code, P = Psyllium Husk powder, $NaHCO_3$ = Sodium Bi Carbonate, PVP = Poly Vinyl Pyrrolidone
FLT = Floating Lag Time, FD= Floating Duration, DS = Dimensional Stability

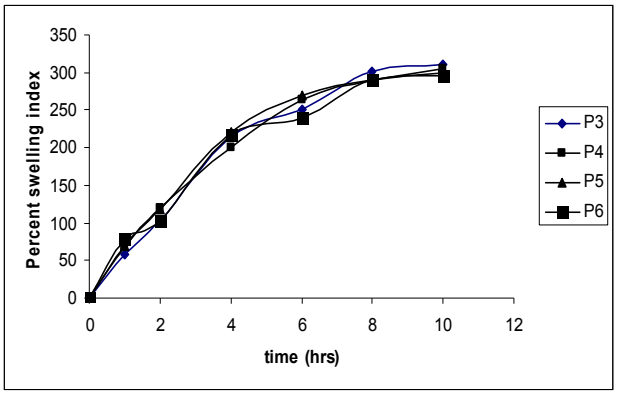


Figure 1. A.Effect of HPMC K 15M on Swelling Index of formulations prepared with Psyllium Husk

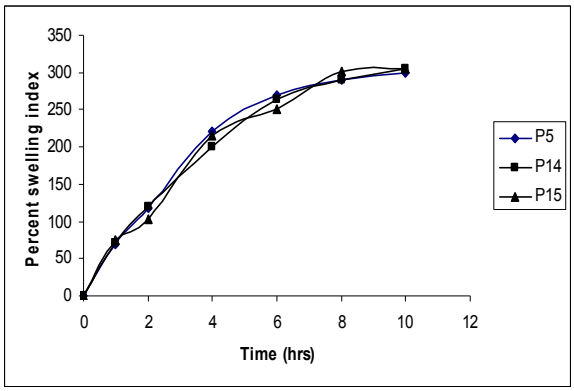


Figure 1.B.Effect of Ac-Di-Sol on Swelling index of formulations prepared with Psyllium Husk

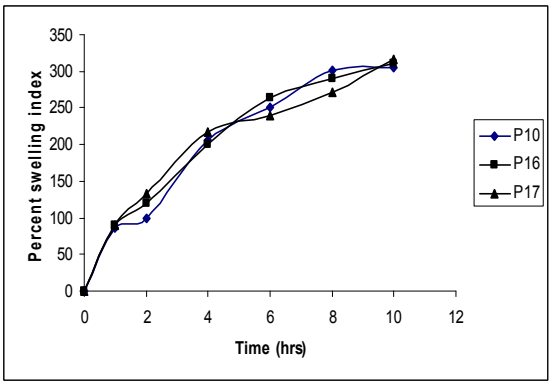
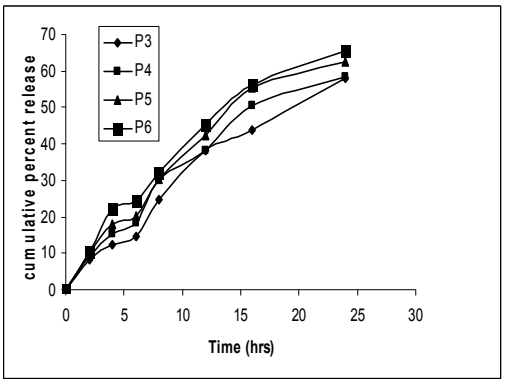
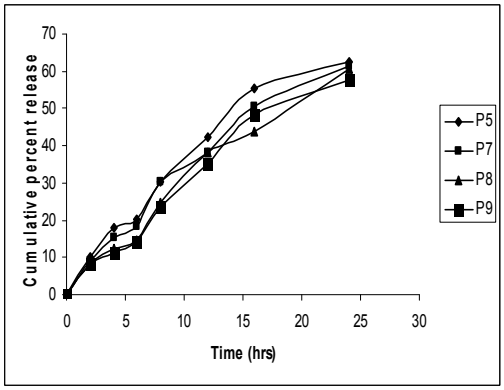


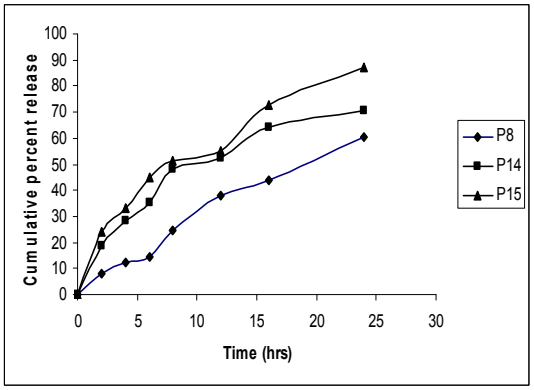
Figure 1.C.Effect of Ac-Di-Sol on Swelling index of formulations prepared with HPMC K 100M



A. Effect of HPMC K15M

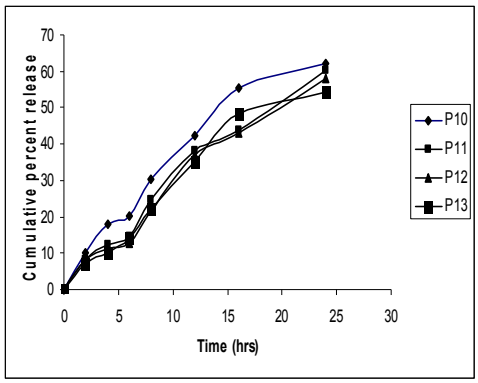


B. Effect of Sod. Bicarbonate

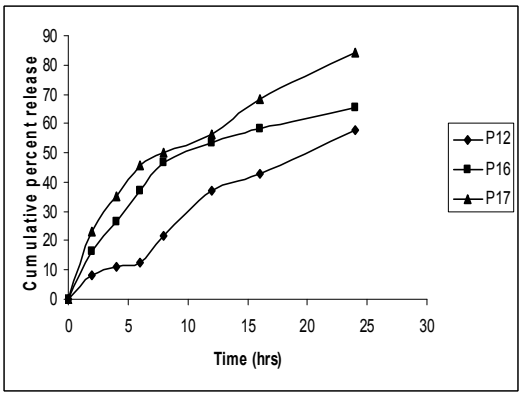


C. Effect of Ac-Di-Sol

Figure 2. *In- vitro* release profile of theophylline from Floating matrix tablets prepared with psyllium in 0.1 N HCL dissolution medium



A. Effect of Sod. Bicarbonate



B. Effect of Ac-Di-Sol

Figure 3. *In- vitro* release profile of theophylline from Floating matrix tablets prepared with HPMC K100M in 0.1 N HCL dissolution medium

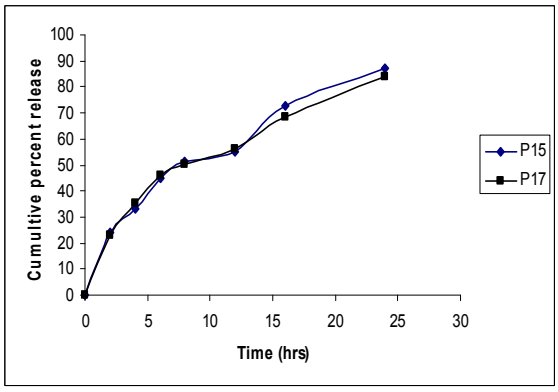


Figure 4. Comparative *In- vitro* release profile of theophylline from optimized floating matrix tablets in 0.1 N HCL dissolution medium

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