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Swelling Approach A Novel Method For Gastric Retention

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ABSTRACT

Present investigation deals with the preparation and characterization of swellable gastroretentive drug delivery system of Pregabalin containing Psyllium Husk, HPMC K4M, Crosspovidone and Polyvinylpyrolidone, as the polymers. The swellable gastroretentive drug delivery system tablets were prepared by wet granulation method. Nine formulations were developed which differed in the ratio of polymers. Formulations PRF-1, PRF-2, PRF-3, PRF-4, PRF-5, PRF-6, PRF-7, PRF-8 and PRF-9 were composed of Psyllium Husk, HPMC K4M, Crosspovidone and Polyvinylpyrolidone respectively. All the formulations were evaluated for swelling index, Mucoadhesive Strength, Mucoadhesive force, Mucoadhesive time and *in vitro* drug release study. In vitro drug release study was performed using United State Pharmacopoeia (USP) type 2 dissolution test apparatus employing paddle stirrer at 50 rpm using 900 ml of 0.1N HCl maintained at 37ºC ± 0.5ºC as the dissolution medium. On the basis of evaluation parameter formulation PRF-5 was selected as developed formulation. Therefore, it can be concluded that the swellable gastroretentive drug delivery system may be exploited successfully for the delivery of drugs such as Pregabalin.

KEY WORDS: Swellable, Gastroretentive, Mucoadhesive.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process[1]. Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. To overcome this problem, gastroretentive drug delivery systems which provide effective plasma drug concentration for longer periods thereby reducing the dosing frequency are being formulated. It also has an advantage of minimising the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner [2]. The retention of oral drug dosage forms in the stomach is improved by using swellable dosage forms that are shaped in a manner that will prevent them from inadvertently passing through the pylorus as a result of being in a particular orientation [3].

Pregabalin (PGB), (S)-3-(aminomethyl)-5-methyl hexanoic acid is an antiepileptic and structurally related to the inhibitory neurotransmitter aminobutyric acid (GABA). It is a white crystalline solid with molecular formula C8H17NO2, molecular mass of 159.23 g/mol and melting point from 190°C to 192°C. It was approved in the year 2007 for adjunctive treatment of partial seizures in adults in United States and Europe, and for the treatment of neuropathic pain from post-therapeutic neuralgia and diabetic neuropathy.[4]

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MATERIALS AND METHODS

Materials

Pregabalin pure was obtain from Alkem Laboratories Ltd, Mumbai, as a gift sample. Psyllium husk was obtained from Alkem Laboratories Ltd, Mumbai, HPMC K4M, Crosspovidone and Polyvinylpyrolidone (PVP K30) were obtained as a gift sample from Ajanta Pharma Aurangabad. All other ingredients were of analytical grade.

Preparation of Swellable Gastroretentive Drug Delivery System [5]

Psyllium husk was triturated for size reduction. All the ingredients were accurately weighed and sieved through sieve no. 60. In order to mix the ingredients thoroughly, drug and all the excipients except the lubricant (magnesium stearate) were blended geometrically in mortar and pestle for 15 minutes and granulated using PVP K30 dissolved insufficient isopropyl alcohol by passing through sieve no.12. Granules were dried at 45°C for 4 h. The dried granules were sized through

Table 1: Composition of Swellable Gastroretentive Drug Delivery System formulations.

Sr.No	Ingredients (mg)	Batches								
		PRF-1	PRF-2	PRF-3	PRF-4	PRF-5	PRF-6	PRF-7	PRF-8	PRF-9
1	Pregabalin	150	150	150	150	150	150	150	150	150
2	Psyllium Husk	100	100	100	200	200	200	200	150	150
3	HPMC K4M	280	260	230	230	260	200	230	260	230
4	Crosspovidone	100	150	200	100	100	200	100	150	150
5	Polyvinylpyrolidone	60	70	50	60	70	50	60	50	70
6	Magnesium stearate	30	40	50	30	40	50	30	40	50
7	Microcrystalline cellulose	100	100	100	100	100	100	100	100	100
8	**Total**	**820**	**870**	**880**	**870**	**920**	**950**	**870**	**900**	**900**

sieve no. 18 and lubricated by adding magnesium stearate. This blend was then compressed in Karnavati tablet compression machine having 8 stations and with the punch 12 mm S.C.

Ex-vivo Mucoadhesion time: [6]

It was determined using a modified USP disintegration apparatus. The disintegration medium composed of 900 ml simulated saliva fluid pH 6.8 maintained at 37 °C. A segment of porcine buccal mucosa, 2 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive film was hydrated from one surface using 1ml simulated saliva fluid and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was calculated.

Ex-vivo Mucoadhesive force:[7]

Tensile strength requires detaching the bioadhesive film for the mucosal surface was applied as a measure of the bioadhesive performance. The apparatus was locally assembled and was a modification of apparatus previously applied by Parodi et al. The device was mainly composed of two-arm balance. At the left arm of balance, movable platform was maintained in the bottom in order to fix the mucosal membrane. For the determination of Bioadhesion force, the bovine buccal mucosa was excised by removing underline connective and adipose tissue and equilibrated at $37^0c \pm 1^0c$ for 30 min. in phosphate buffer pH 6.8. To the right side pan film was attached with double adhesive tape and wetted with the 50µl of pH 6.8 simulated phosphate buffer, the pan was placed on the bovine buccal mucosa which is already fixed with clamp. Weight of 50 gm was applied for 20 sec. and the weight required to detach the patch from mucosa was measured.

Mucoadhesive force = (W×g) / A

Where W is minimum weight required to break the bioadhesive bond (g)

g is acceleration due to gravity ($cm.s^{-2}$)

A is the surface area of the patch (cm^2)

Detachment Force Measurement /Mucoadhesion Strength [8]

To characterize the mucoadhesive strength, the detachment force method can be used (Figure 1). Collect goat intestine from slaughter house and transfer to tyrode solution. During this experiment the intestine have to place on one glass slide and tied on both side of the assembly. Affix glass slide with the intestine on one side floor below the modified physical balance. Past the mucoadhesive agent tablet on another glass slide and balanced on the assemble physical balance with a beaker on other side which can be used to hold the water, amount of water in gram which require to detach the tablet were recorded.

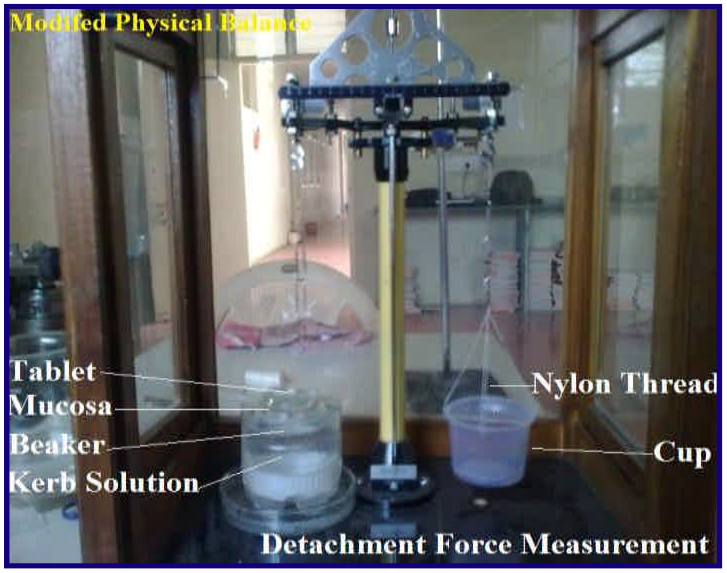

Figure 1: Mucoadhesive Strength Measurement by Detachment Force Measurement

Swelling Index: [9] The swelling of the polymers can be measured by

their ability to absorb water and swell enormously. The swelling index is the ability of the polymers to swell by absorbing water. The water uptake study of the tablets was carried out by using USP dissolution apparatus type-II. The medium used was 900 ml of distilled water. The testing was carried out at rotation speed of 100 rpm. The temperature of the bath and medium was maintained at 37 ± 0.50 C throughout the study. The tablets were placed in the medium under rotation. The tablets were withdrawn from the medium after selected time interval, excess water removed by blotting and weighed. The swelling index of the tablets was given by following formula:

$$\text{Swelling index (\%)} = \frac{\text{Weight of swollen tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

In-vitro dissolution studies: [10] The release rate of Pregabalin from matrix tablets was determined using USP dissolution testing apparatus type-II (Paddle type). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 50 rpm. A 5ml sample solution was withdrawn from the dissolution apparatus at predetermined time interval of 1, 2, 4, 6, 8, 12, 16, 24 hours and diluted when necessary. The medium were replaced with 5 ml of fresh 0.1N HCl after each sampling. The amount of Pregabalin dissolved at various time intervals was determined by employing U.V Spectrophotometer absorption at the wavelength of ?max 210 nm.

Drug release kinetics: [11, 12, 13, 14] In order to investigate the drug release mechanism from tablets, the % cumulative drug release data was analyzed with following mathematical models

Model	Equation
Zero order kinetics	Q = Qo - Kot
First order kinetics	Q = Qo (1 - e-K1t)
Higuchi square root model	Qt = KH t ½
Hixson-Crowell cube root model	- = KHCt
Korsmeyer- peppas model	Qt/ Q8= Kktn

Where, Qt - amount of drug released at time t. Qo - initial amount of drug. And Ko, K1, KH, KHC and KK are the coefficients of equations. The most appropriate model was selected on the basis of goodness of fit test. The zero order kinetic describes the systems in which the drug release rate is independent of its concentration. The drug releases slowly (assuming that the area does not change and no equilibrium conditions are obtained). The first order kinetics describes the systems in which drug release rate is concentration dependent. Higuchi model describes the release of water-soluble drug from an insoluble matrix as a diffusion process based on the Fick's law and is square root time dependent. The Hixson-Crowell cube root law describes the drug release from a system depends upon the change in surface area or diameter of particle or system and involves no diffusion mechanism. Korsmeyer-Peppas model describes the fraction of drug release relates exponentially with respect to time. This model is generally 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 phenomena could be involved. Drug release kinetics and best fit model for all the selected batches was found out with the help of PCP DISSO Software V 2.08 and Microsoft Excel.

RESULT & DISCUSSION

Mucoadhesive Strength, force of adhesion and Mucoadhesion Time. Psyllium husk and HPMC K4M has been reported to possess good mucoadhesive properties. When these polymers come in contact with water forms mucilage and swells, thus are responsible for mucoadhesion by simple bonding with mucus components. Mucoadhesion strength and mucoadhesion force were found good enough (23.7- 31.5 gm and 2.32 – 3.09 N). Mucoadhesion Time was found in the range of 6 to 11 hrs. Based on the results of mucoadhesion study it can be predicted that gastric retention has been achieved. The results are shown in Table 2.

Table 2. Mucoadhesive Strength, force, Mucoadhesive time and Swelling for all the Preliminary batches.

Sr. No	Batch Code	Mucoadhesive Strength (gm)	Mucoadhesive force (N)	Mucoadhesive Time
1	PRF-1	27	2.64	More than 9.5 hrs
2	PRF-2	31.5	3.09	More than 11 hrs
3	PRF-3	27	2.64	More than 10 hrs
4	PRF-4	27.5	2.69	More than 10.5 hrs
5	PRF-5	29	2.84	More than 11 hrs
6	PRF-6	28	2.74	More than 9.5 hrs
7	PRF-7	27	2.64	More than 10 hrs
8	PRF-8	23.7	2.32	More than 6 hrs
9	PRF-9	26	2.55	More than 9.2 hrs

Swelling Study:- The swelling of the polymers is studied by their ability to imbibe water and swell enormously. In the present study polymers used in the formulation HPMC K4M, Psyllium husk have been reported to show good swelling properties. These polymers in combination showed good swelling properties ranging from 203% to 232 %. This increase in swelling was possible only due to imbibitions and mucilage formation of polymers when it comes in contact with biological and or aqueous medium and due to which swelling took place. Based on the results of swelling index it can be predicted that gastric retention can be achieved preferably more than 24 hrs. The results are shown in Table 3 and Figure No.2.

Table 3: *In-vitro* swelling index of pregabalin sustained release tablet for all batches

Sr. No	Batches	Initial Weight (mg)	Weight After Swelling (mg)	% Swelling
1	PRF-1	820	2665	225
2	PRF-2	870	2540	192
3	PRF-3	880	2680	205
4	PRF-4	870	2860	229
5	PRF-5	920	3055	232
6	PRF-6	950	2880	203
7	PRF-7	870	2697	210
8	PRF-8	900	2817	213
9	PRF-9	900	2863	218

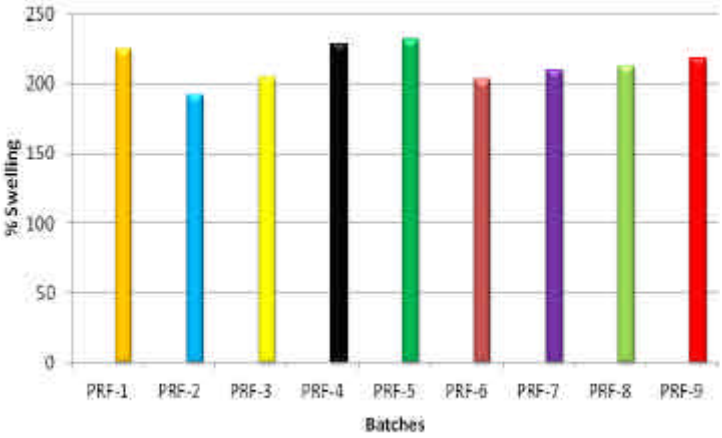

Figure 2. Swelling Study for all Batch

In-Vitro Dissolution Study: The PRF-5 batch showed highest drug release i:e 95.3% upto 24 hrs, this was possible due to optimum concentration of all the polymers used in the formulation of the swellable gastroretentive dosage form. The results are shown in table No.4 and figure No.3 & 4 .

Table 4: In-vitro dissolution study for all the batches.

Sr.No	Time (hrs)	Cumulative % Drug Release For All Batches PRF-1	PRF-2	PRF-3	PRF-4
1	0	00	00	00	00
2	1	8.2	11.4	14.7	12.1
3	2	13.2	19.3	23.6	17.9
4	4	34.6	39.4	29.7	25.7
5	6	41.3	57.1	39.6	37.2
6	8	54.4	65.4	54.1	48.8
7	12	65.2	77.6	71.4	68.3
8	16	76.3	86.2	83.5	82.4
9	24	90.4	91.3	92.4	94.1

Sr.No	Time (hrs)	Cumulative % Drug Release For All Batches PRF-1	PRF-2	PRF-3	PRF-4
1	0	00	00	00	00
2	1	8.2	11.4	14.7	12.1
3	2	13.2	19.3	23.6	17.9
4	4	34.6	39.4	29.7	25.7
5	6	41.3	57.1	39.6	37.2
6	8	54.4	65.4	54.1	48.8
7	12	65.2	77.6	71.4	68.3
8	16	76.3	86.2	83.5	82.4
9	24	90.4	91.3	92.4	94.1

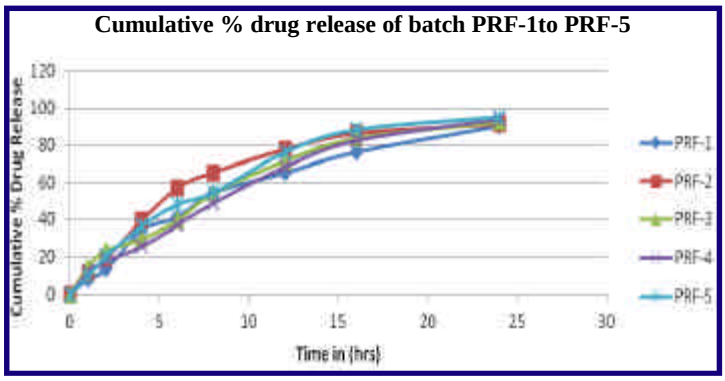

Figure 3: *In-vitro* dissolution profile of pregabalin sustained release tablet PRF-1 to PRF-5

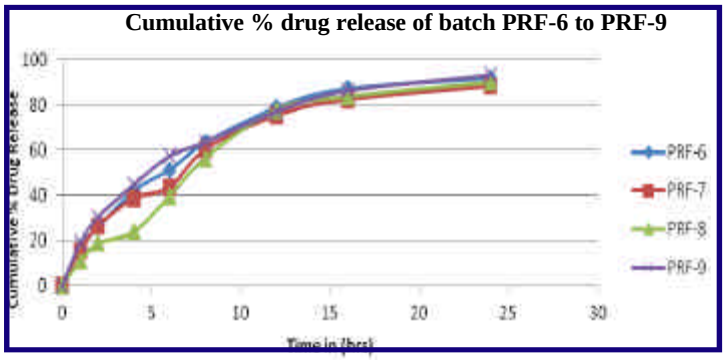

Figure 4: *In-vitro* dissolution profile of pregabalin sustained release tabletPRF-6 to PRF-9

Drug release Kinetics: The rate constants for *in vitro* release study of swelling drug delivery systems, by using PCP Disso software V2.08 and Microsoft excel.

% Release (Average) with model fitting		
Name of the Drug = PREGABALIN	Batch = PRF-5	Date = 25/02/2012
Loading Dose in mg = 150		
Total no. of Readings, including 'Zero-time' reading = 9		Done by = SGS
Dissolution Medium =	0.1 N HCL	
RPM =	50	
Volume of Dissolution Medium (ml) =	900	
Volume of Sample removed (ml) =	5	

Table 6: Cumulative % Drug Release (Average) with model fitting

Model Fitting (Average)	R	k
Zero order	0.9096	4.9995
T-test	5.792	(Passes)
1st order	0.9911	-0.1247
T-test	19.742	(Passes)
Matrix	0.9812	19.8247
T-test	13.458	(Passes)
Peppas	0.9972	11.3527
T-test	19.802	(Passes)
Hix.Crow.	0.9910	-0.0288
T-test	19.548	(Passes)
t-Table at P0.05 (Two Tails), DF= n-2:		2.365
Best fit model		Peppas
Parameters for Korsmeyer-Peppas Equation-	**n** =0.7295	**& k** =11.3527

To analyze the release mechanism of pregabalin in vitro release data was fitted into various release equations and kinetic models ((Zero order, First order, Higuchi and Korsmeyer-Peppas) for all the selected batches. From this it was found that the passage of drug through the hydrated gel matrix tablet is dependent on the square root of time. When the release profile was plotted versus square root of time, a linear relationship was observed with the regression coefficient close to one. In the controlled or sustained release formulations diffusions, swelling and erosion are the three most important rate controlling mechanism followed. The drug release from polymeric system is mostly by diffusion and is best described by Fickian diffusion. But, in the case of formulation containing swelling polymers, other processes in addition to diffusion play important role in exploring the drug release mechanism. These processes include relaxation of polymer chains, imbibitions of water causing polymers to swell. Due to swelling, considerable volume expansion take place leading to moving diffusion boundaries complicating the solution Fick's second law of diffusion. The release is treated by Korsmeyer and Peppas equation Qt/ Q8= Kktn Where Qt = Drug released at time t, Q8 = amount of drug released at infinite time, K = Kinetics constant, n = diffusional exponent. The equation was used to determine the value of release exponent, *n*; the value of n is indicative of mechanism of drug release. When n takes the value of 0.5 it indicates diffusion controlled release and for the value 1 it indicates swelling controlled drug release. A value of *n* in between 0.5-1 represents the release mechanism by diffusion as well as swelling (anomalous transport). The optimized formulation PRF-5 shows n value of 0.7295and R2 value of 0.9972.Hence it can be concluded that the optimized formulation obeys Korsmeyer-Peppas release kinetic model. The results are shown in table No.6 & Figure No. 5.

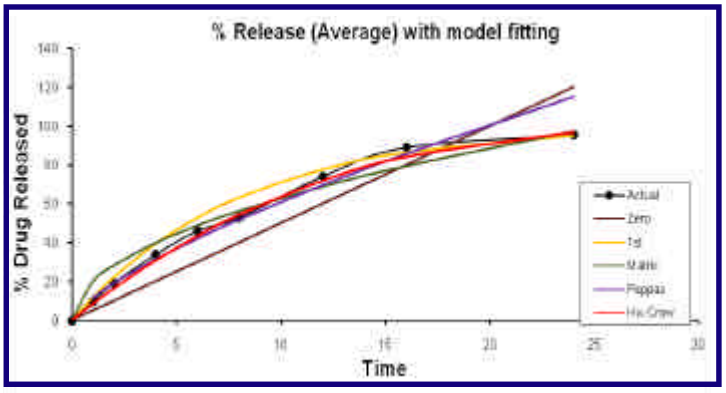

Figure 5: Cumulative % Drug Release (Average) with model fitting

CONCLUSION:

From the above study it can be as the batch PRF-5 showed best results for mucoadhesion strength, mucoadhesion time, mucoadhesion force, Swelling study and In-Vitro dissolution, the polymers like psyllium husk, HPMC K4M, Crosspovidone and Polyvinylpyrolidone in combination can be promising polymers for gastroretentive drug delivery systems. The optimized formulation followed Korsmeyer-Peppas while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix. Swelling studies were indicated significant water uptake and contributed in drug release and could be significant in gastro-retention. The optimized formulation PF-5 shows n value of 0.7295and R^2 value of 0.9972.

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