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Designing and In-Vitro Evaluation of Gastro Retentive Drug Delivery System for Pregabalin

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Abstract: Sustained release gastro retentive 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 present study was to develop once daily SR floating matrix tablet for Pregabalin using HPMC K4M as rate controlling polymer, ethyl cellulose as a coating polymer & crospovidone as a swelling agent were 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, high viscosity grades of HPMC K4M were show appropriate result in lesser concentration as compare to low viscosity grades which require higher concentration for developing stable formulation. The release rate of optimized formulation was matching with released rate of marketed preparation & with theoretical profile also. The in vitro release data and drug release mechanism of the optimized formulation followed the Korsmeyer-peppas model and non-fickian mechanism. Hence It can be concluded that, higher viscosity grade of HPMC K4M, crospovidone, along with ethyl cellulose have more release retarding capacity & these can be a promising polymer for gastroretentive floating drug delivery systems in combination.
Keywords: Pregabalin, Floating matrix, Gastroretentive, Sustained release, HPMC K4M.

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 of GRDDS are as

1) Floating i.e. Effervescent Systems and non effervescent Systems,
2) Swelling or expendable,
3) High density system
4) Inflation and Bio-adhesion system 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 aim or objective of this study was to prepare a sustained release floating drug delivery system of Pregabalin using synthetic polymer as rate controlling polymer. HPMC K4M & crospovidone possesses good gelling & swelling properties respectively, therefore ,when used as matrix forming agent in modified release forms a swollen gel by the time ,thus it is able to controlled drug release. Pregabalin is used for the treatment of certain type of peripheral neuropathic pain & in therapy of partial seizures of epilepsy & also for generalized anxiety disorder. It is also used in post herpetic neuralgia a complication of Herpe-Zoster. Thus for these chronic condition ,it is more suitable to formulate sustained release formulation & avoiding frequent dosing .Also Pregabalin is mainly absorbed in stomach & to some extend in upper part of small intestine, so retention of drug in the stomach will be beneficial to improve the absorption of the drug(where it is in unionized form) [9, 10,11].

Materials And Methods:

Pregabalin (Kopran Pvt Ltd, Mahad), HPMC K4M (Colorcon, Mumbai), Crospovidone (BASF, Switzerland), Ethyl Cellulose (Aqualon Hercules, USA), Avicel 105 (FMC Biopolymer, USA) Talc(Nilkanth Minechem & S kant healthcare, India) etc. All these chemicals were analytical grades.

Fabrication of Floating Matrix Tablet

Different batches of floating matrix tablets were prepared by wet granulation method. Firstly all powder passed through sieve no.#80 ASTM ,then the respective powder of drug & polymer with other ingredient were blended thoroughly & dump mass was prepared by adding in IPA. The wet granules were passed through sieve no. #12 ASTM & drying was carried out in tray dryer at 45^0 c. All dried granules were passed through sieve no. #18 ASTM. Talc was passed through sieve no.#60 ASTM & mixed with dried granules. This blend was then compressed in Cadmach machine having 16 stations & with Punch 13.5mm SC(standard concave). The tablet hardness was maintained in range of 3-6 Kg/cm^2

Buoyancy Capacity

The buoyancy 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 buoyant on the surface of the medium (duration of buoyancy) was observed visually.

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 Pregabalin tablets was observed visually.

Determination of Swelling Index(Water Uptake)

The water uptake or 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 ± 0.5^0C and rotation speed 100 rpm.

The swelling index was calculated by the following formula:

Swelling index = (Wt – Wo / Wo) × 100

Where:

Wo = the initial weight of matrix tablet.

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

In-Vitro Release Study

The release of Pregabalin from the matrix tablets was determined using the USP dissolution apparatus II in 900ml 0.1 N HCl at 37 ± 0.5^0C. The rotation speed was 100 rpm. 5 ml of aliquot was withdrawn from dissolution apparatus at predetermine intervals, and medium was replenished with 5 ml of fresh medium at each time interval. The amount of Pregabalin dissolved at various time intervals was determine by employing HPLC with UV spectrophotometer(Shimadzu 2100, Japan)detector at 210 nm on test solution in comparison with standard solution.

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

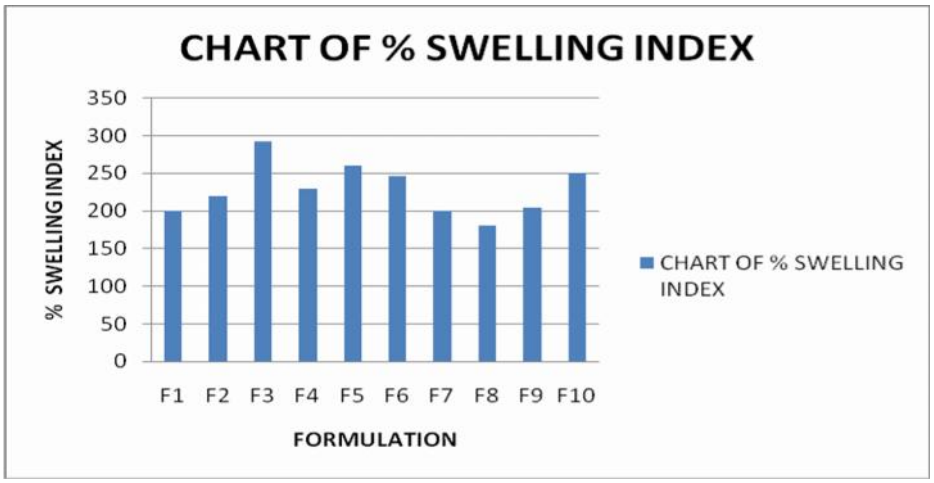
regular contraction termed as housekeeper waves that swept out the particulate matter (undigested food particles) from the stomach and lasts to 10 to 20 minutes. To prevent the formulation from the effect of this phase, tablet should be float as fast as possible after reaching in the stomach. In similar 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 buoyancy lag time decreases as the concentration of HPMC K4M & crospovidone increases, whereas incase of duration of buoyancy & dimensional stability were observed as constant(24 hr) for all formulation containing HPMC K4M (2500 cps) concentration 35-45%.Afterwords when work proceeded with HPMC K4M(3500 cps), in that case also no any changes in duration of buoyancy & dimensional stability were observed & so it was concluded that concentration range above 35% HPMC K4M(3500 & 2500 cps) polymers useful for development of sustained release gastroretentive drug delivery system. The buoyancy lag time also depend on hardness, as the hardness increased, the buoyancy lag time also increased, 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 they come in to contact with the gastric fluid and as a result, the capability of the tablets to float is significantly reduced.

Swelling/Water Uptake Study :-

The swelling of the polymer was determined by water uptake of the tablet. The percent swelling of tablet was determined by the method described in previous. The percent swelling of optimized formulation F10 was found to be higher than that of marketed formulation. There was significant increase in percent swelling of the tablet with increase crospovidone concentrations. Similarly increasing concentration of HPMC K4M(2500 & 3500 cps) also showed increase in swelling but not to that extent of crospovidone as it's mainly used as a release retarding agent here. In all the formulations maximum swelling was observed in 8hrs. With a very sharp increase up to 4h in all the concentrations containing crospovidone. The swelling index of formulation as shown in the table no-1. The percent swelling then gradually increased up to 8h and then gradually decreased till 24h. Also the release retarding polymers like HPMC K4M definitely have contributed in swelling properties apart from their release retarding property. HPMC K4M(3500 & 2500 cps) swell immediately while crospovidone swell completely in 3-4 hours this could be the reason that the faster swelling occurs in about 4 hrs with complete swelling in 8h.At the end of 4hrs the Tablet was swollen almost to its maximum volume. Also higher water content could predict the higher penetration of the gastric fluid into the tablet. Consequently, faster and higher swelling of the tablet to increase in dimensions of the tablet leading to increasing diffusion pathways and thus decreasing diffusion rates. So the drug release was found high initially and then decreases gradually and complete release was obtained in 24h**.**

Table no-1: Swelling/Water Uptake Study

Formulations	Initial Weight(Wo)mg	Weight After Swelling (Wt)mg	% Swelling
F-1	650	1950	200
F-2	655	2207	220
F-3	649	2550	292
F-4	651	2153	230
F-5	653	2307	260
F-6	652	2256	246
F-7	648	1950	200
F-8	653	1836	180
F-9	650	1985	205
F-10	652	2288	251
Markected preperation	647	2190	236



Graph No-1: % Swelling Index Data of selected batches.

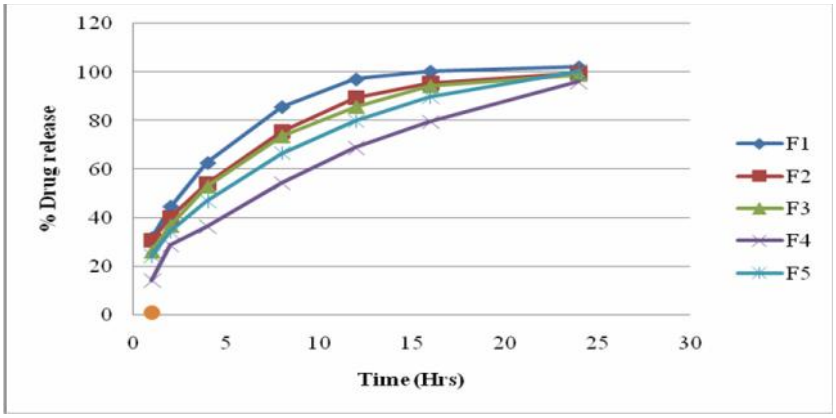
In-vitro *R*elease Study

Developed batches from F1 to F4 were formulated with HPMC K4M(2500 cps) with varying concentrations and fix concentration of crospovidone and ethyl cellulose . The in vitro release profile of these batches is given in the table. In the drug release data, it is found that, the concentration of HPMC K4M(2500 cps) should be optimized for proper release of the drug, swelling and integrity of formulation. Batch F1 which contained the low polymer concentration(30%) shows release of the drug fastly because of the poor strength of the matrix, but as the concentration of HPMC K4M(2500 cps) was increased in batch F2 (35%) the release was decreased from the previous but desired release with the theoretical release profile was not there and further increased in concentration of HPMC K4M(2500 cps) in batch F3(40%), initial release decreased , also the other time point concentration also got decreased. Further increase in the concentration of HPMC K4M(2500 cps) in F-4(45%) shows drastic decrease in initial release, so in next formulation, the concentration of HPMC K4M (2500 cps) decreased F5(42%) which shows good resemblance with the theoretical release profile and also shows good matrix strength with crospovidone.

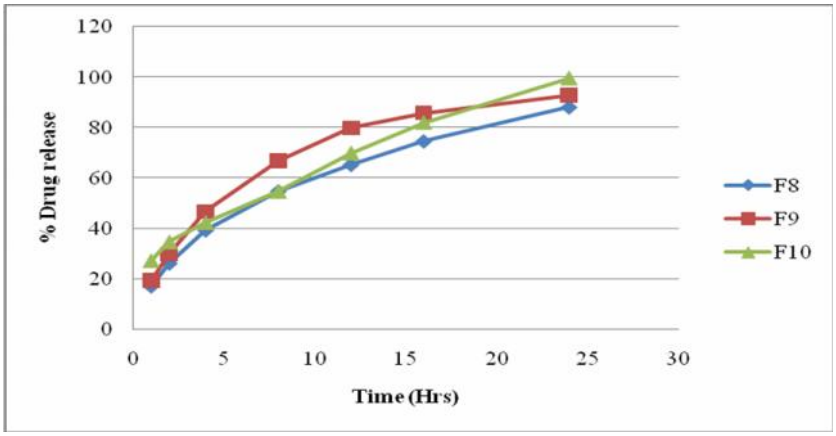
The batch F1 indicates that matrix strength was not good & the release was also fast, but able to hold the matrix intact, but as the concentration of HPMC K4M(2500 cps) was increased in batch F2 the release was upto 99 % in 24 hr but the initial release was fast. Further increase in the concentration of HPMC K4M(2500 cps), decreased the drug release as in batch F3 but here the rate was slower than F-2, on further increase in concentration of HPMC K4M (2500 cps) in F-4 initial release decreased drastically so finally F-5 was selected for the further development as it has shown more resemblance with the theoretical release profile. Developed batches from F5 to F7 were form with HPMC K4M(K4M) for the optimization of Crospovidone in presence of Ethyl cellulose. The in vitro release profile of these batches is given in the table. In the drug release data, it is found that as the concentration of Crospovidone has to be optimum for maintaining the matrix integrity along with the resemblance with in-vitro theoretical release profile. In the batch F-5, it was found that the initial release was fast but not sufficient to provide loading dose and also the total release was 100.5% where the concentration of the crospovidone was 15%,With further increase in the concentration of crospovidone, the initial release was achieve the loading dose level along with the final result of 98.6%, on further increase in crospovidone concentration to 25% shows the decrease in initial release as well as total release .Hence the 20% concentration of the crospovidone was optimized for better release property and for keeping the matrix intact along with HPMC K4M (2500 cps) and ethyl cellulose. Afterwords it was observed that viscosity of polymer also have impact on drug release which was observed when polymer grade from HPMC K4M(2500 cps) change to HPMC K4M(3500cps) due to supplier. Developed batches from F8 to F10 were formulated with HPMC K4M(3500 cps) with varying concentrations and optimized concentration of crospovidone and fixed concentration of ethyl cellulose from literature . The in vitro release profile of these batches is given in the table .Batch F8 which contained the optimized concentration of HPMC K4M(3500 cps)(42%)shows release of the drug decreased

because of the higher strength of the matrix due to high viscosity grade, but as the concentration of HPMC K4M(3500 cps) was decreased in batch F9 (40%) the release was increased from the previous but desired release with the theoretical release profile was not there and thereafter further decreased in the concentration of the F-10 (35%) shows resemblance with result which where observed with 42% HPMC K4M(2500 cps) & having close resemblance with the theoretical release profile and also shows good matrix strength with crospovidone.

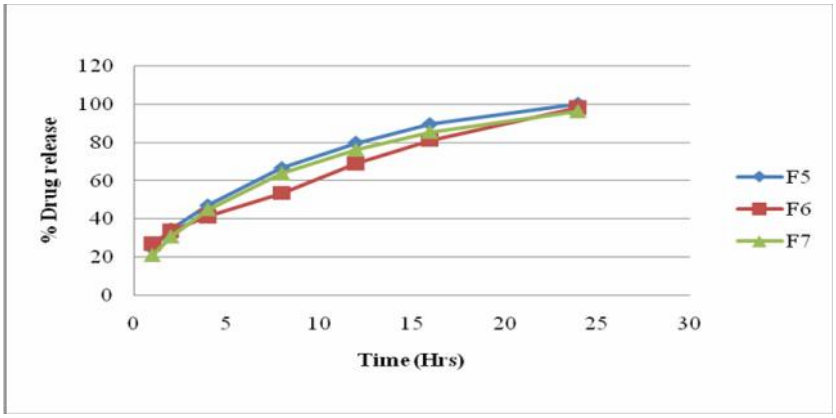
From the batch F8, it is clear that, with 42% HPMC K4M(3500 cps) matrix strength was too high so the drug release was slow & hold the matrix intact, but as the concentration of HPMC K4M(3500 cps) was decreased in batch F9 to 40% , the release increased but the initial release was still slow, so finally the formulation F10 containing HPMC K4M(3500 cps) (35%) was selected for the further development as it has shown more resemblance with the theoretical release profile.



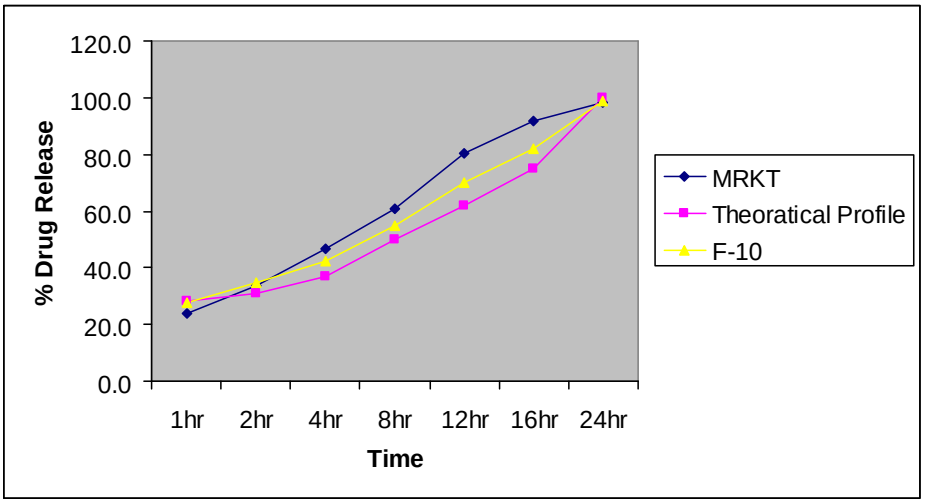
Graph no-2: In vitro release profile to study the effect of HPMC K4M(2500 CPS) F-1toF-5.



Graph No-3: In vitro release profile to study the effect of HPMC K4M(3500 CPS) F-8toF-10.



Graph No-4: In vitro release profile to study the effect of Crospovidone in selected batches F5 to F7.



Graph No-5: In-vitro Release of F-10 with Marketed preparation and Theoretical release profile.

Table No-2: Evaluation Parameter

F.C	Pregabalin (%)	HPMC K4M (2500 cps)(%)	HPMC K4M (3500cps) (%)	Cross povidone (%)	Ethyl Cellulose (%)	BLT	BD	DS	Drug Release (24 Hrs)	S.I
F1	**27.4**	**30**	**-**	**15**	**4**	**06**	**24**	**24**	**102.1**	**200**
F2	**27.4**	**35**	**-**	**15**	**4**	**05**	**24**	**24**	**99.6**	**220**
F3	**27.4**	**40**	**-**	**15**	**4**	**03**	**24**	**24**	**98.9**	**292**
F4	**27.4**	**45**	**-**	**15**	**4**	**01**	**24**	**24**	**96.1**	**230**
F5	**27.4**	**42**	**-**	**15**	**4**	**02**	**24**	**24**	**100.5**	**260**
F6	**27.4**	**42**	**-**	**20**	**4**	**01**	**24**	**24**	**98.6**	**246**
F7	**27.4**	**42**	**-**	**25**	**4**	**01**	**24**	**24**	**96.5**	**200**
F8	**27.4**	**-**	**42**	**20**	**4**	**04**	**24**	**24**	**88.2**	**180**
F9	**27.4**	**-**	**40**	**20**	**4**	**03**	**24**	**24**	**92.8**	**205**
F10	**27.4**	**-**	**35**	**20**	**4**	**01**	**24**	**24**	**99.7**	**251**

F.C=Formulation Code, BLT=Buoyancy Lag Time, BD=Duration of Buoyancy, DS=Dimension Stability, S.I=Swelling Index.

Release Kinetics*:*

To analyze the release mechanism of Pregabalin the *in vitro* release data were 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

$M_t / M_\infty = Kt^n$;

Where M_t = Drug released at time t, M_∞ = 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).

As indicated by values of R^2, the matrix model was found to be efficient in describing the kinetics of Pregabalin release from the floating tablet formulations, with the drug release being proportional to the square root of release time. To explore the release pattern, results of in-vitro release data of all selected formulations were fitted to Korsmeyer and Peppas equation which characterize the transport mechanism.

Stability Batch Studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The Stability studies were performed on the most promising tablet formulation F-10.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and enables recommended storage conditions and shelf lives to be established. The condition and time duration for these studies as per ICH Q1A (R2) guidelines. The stability studies are performed by keeping the Final formulation in the Aluminum pouch at the following condition for specified time.

Observation: The stability studies show that the formulation was under accelerated condition as the assay,Dissolution profile were maintained with the initial formulation.Also the physical parameters swelling index, hardness,frialility were also maintained under accelerated condition.Hence,it can found that the F-10 formulatin is stable.

Table 3: Stability studies data.

Sr. No.	Characteristics	40°75% 0 month	40°75% 1 month	40°75% 2month
1	Group Weight of 20Tabs.	12.998±0.04	12.992±0.04	12.792±0.02
2	Color	White to Off- White	White to Off- White	White to Off- White
3	Hardness	4.69 kg/cm^2	4.63 kg/cm^2	4.45 kgf
4	Friability	0.54%	0.51%	0.53%
5	Swelling Index	248%	245%	241%
6	Dissolution	98.84%	98.60%	98.23%
7	Assay	100.49%	100.20%	100.15%
8	Moisture content	4.35%	4.76%	5.10%

Conclusion

Thus from the whole research work it can be concluded that the objective of the proposed project has been fulfilled and GRDDS for Pregabalin using HPMC K4M (2500 & 3500 cps) have been successfully formulated and evaluated. The conclusion of the studies can be summarized as:

HPMC K4M(2500 & 3500 cps) might be a promising polymer for gastroretentive floating drug delivery systems. Use of HPMC K4M(2500 & 3500 cps) with ethyl cellulose enhanced the floating duration and help to maintain the dimensional stability at initial stage, which is necessary in case of once daily formulations. Crospovidone used to improve the release profile. Optimized formulation followed the Korsmeyer-peppas kinetics while the drug release mechanism was found to be anomalous types or non-fickain type & controlled by diffusion through the swollen matrix. Optimized formulation shows good drug released result than marketed (Intas) formulation & also found to be stable at all stability conditions (2 month data available).

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