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A REVIEW ON FORMULATION & IN-VITRO CHARACTERIZATION OF THE MUCOADHESIVE GASTRO-RETENTIVE TABLET OF PREGABALIN

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ABSTRACT

The aim of this investigation was to formulate gastroretentive tablets of pregabalin utilizing the potential of natural gums as mucoadhesive polymer so that the formulation could control the release of the drug thereby reducing its dosing frequency and improving the bioavailability. The angle of repose, bulk density, tapped density, Hausner's ratio and Carr's Index were found to be ranging from 23.78 ± 0.5468° to 26.54 ± 0.2939°, 0.39 ± 0.0435 to 0.533 ± 0.0208 g/cm^3, 0.476 ± 0.0152 to 0.596 ± 0.0251 g/cm^3, 1.05 to 1.24 and 4.82 to 19.38 respectively. The thickness of tablets was 4.9 to 4.8 mm, hardness 4.5 kg/cm^2 and 4.1 kg/cm^2, friability 0.19% to 0.49% and the weight variation 1.8 to 1.2%. Swelling study was performed on all the formulation for 9 h and was found to be in the range of 2.23 to 6.08. The highest degree of swelling was achieved by F7 containing a mixture of all the three gums. All the formulations were able to prolong the release of drug for more than 10 hours. Formulation F6 and F7 were able to sustain the release to higher duration with F6 and F7 releasing 87.2 and 81.6% pregabalin respectively at the end of the 12 hours of study.

KEYWORDS: Pregabalin, sustained release, gastroretentive, mucoadhesion, natural gum.

INTRODUCTION

Oral Drug Delivery

Development in pharmaceutical technology has provided viable dosage alternatives that can be administered via different routes of administration. Various routes that are used include oral, parenteral, topical, nasal, rectal, vaginal and ocular (Bhardwaj et al., 2011). To date, oral administration is the most convenient and preferred route of any drug delivery to the systemic circulation (Kumar et al., 2013). This is because the oral route provides ease of administration, more flexibility in designing, ease of production and low cost (Bhardwaj et al., 2011). Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems (Sarojini & Manavalan, 2012).

The Gastro-intestinal Tract and Drug Delivery

Drugs administered orally pass through and are absorbed along the gastrointestinal tract (GIT). The GIT is essentially a tube of about nine metres that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum) (Kumar et al., 2013) (Figure 1.1). The GIT is a continuous muscular tube, which functions to take in nutrients and eliminate waste by such physiological processes as secretion, motility, digestion, absorption and excretion. The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising of serosa, longitudinal muscle, intermuscular plane, circular muscle, submucosa, muscularis mucosae, lamina propria and epithelium. The GIT presents a large surface area which is a perfect environment for the delivery and absorption of drugs (Zate et al., 2010).

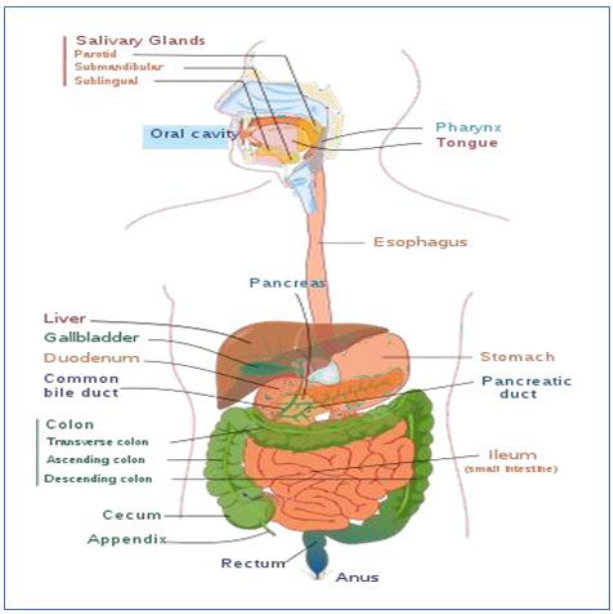

Figure 1.1 Representation of the GIT.

The achievement and maintenance of a concentration of a drug at the appropriate site(s) of action which is both clinically efficacious and safe for the desired duration of treatment is then the aim of drug therapy. Proper selection of the dose size and the dosage time interval is crucial in ensuring that a multiple-dosage regimen provides steady-state concentrations of drug in the body which are both clinically efficacious and safe.

Drugs that are easily absorbed from the gastrointestinal tract and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. Poor patient compliance, unavoidable fluctuations of drug concentration, difficulty in attainment of steady-state condition are some drawbacks associated with the frequent dosing of drugs.

In order to avoid this limitation, the development of oral sustained or controlled release delivery systems is an attempt to release the drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a long time (Badoni et al., 2012).

Gastro-retentive Drug Delivery Systems

Optimum gastro-retentive drug formulations can be defined as systems which are retained in the stomach for a sufficient time interval against all the physiological barriers, release active moiety in a controlled manner, ultimately being metabolized in

the body (Foda & Ali, 2011). Gastro-retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Many drugs categorized as once-a- day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging (Kumar et al., 2013). Prolonged gastric retention therefore helps to improve bioavailability, reduce drug waste, and improve solubility of drugs that are less soluble in a high pH environment (Upadhyay et al., 2014).

Potential drug candidates for Gastro-retentive Drug Delivery

- Drugs acting locally in the stomach such as misoprostol and antacids.
- Drugs those are poorly soluble at alkaline pH such as diazepam, verapamil hydrochloride and griseofulvin.
- Drugs with a narrow window of absorption such as furosemide and riboflavin.
- Drugs which are absorbed rapidly from the GIT such as metronidazole.
- Drugs those are unstable in the intestinal or colonic environment such as captopril and ranitidine.
- Drugs that disturb normal colonic microbes such as antibiotics against Helicobacter pylori (Badoni et al., 2012).

Approaches for enhancing gastric retention

The gastric retention of drugs can be enhanced using one of the several approaches mentioned below.

1. Floating systems

Floating systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system (Figure 1.2). After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

2. Mucoadhesive/Bioadhesive systems

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/mucoadhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

3. Swelling/Expanding systems

These are the dosage forms, which after swallowing swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type system", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. A balance between the extent and duration of swelling is maintained by the degree of crosslinking between the polymeric chains. A high degree of cross- linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

4. High density systems

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach.

Advantages of Gastroretentive systems (Soni et al., 2001)

- It might lead to improvement of bioavailability and therapeutic efficacy of the drugs and possible dose reduction.
- It enables constant therapeutic levels over a prolonged period and thus reduction in

fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics.

- For drugs with relatively short half-life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.
- It can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET).
- It can produce prolonged and sustained release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
- The slow and regulated delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs.
- It can minimize the counter activity of the body leading to higher drug efficiency.
- It causes improved selectivity in receptor activation due to reduction of fluctuation in drug concentration.

Limitations of gastroretentive systems (Dahiya et al., 2011)

- The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
- High turnover of mucus may affect the effectiveness of gastro retention.
- Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
- Not suitable for drugs that may cause gastric lesions or drugs that are unstable in the strong acidic environment.
- The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

Characterization of gastroretentive systems

1. Size and shape evaluation

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation was determined using Sieve analysis, Air elutriation (Bahco TM) analysis, Photo analysis,

Optical microscope, Electro resistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc (Ali et al., 2005).

2. Floating Properties

Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design (Ji et al., 2016).

3. Surface Topography

The surface topography and structures were determined using scanning electron microscope operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer (Zhang and Hongming, 2016).

4. Determination of moisture content

The water content per se is seldom of interest. Rather, it shows whether a product intended for trade and production has standard properties such as:

- Storability
- Agglomeration in the case of powders
- Microbiological stability
- Flow properties, viscosity
- Dry substance content
- Concentration or purity
- Commercial grade (compliance with quality agreements)

Thus moisture content of the prepared formulations was determined by Karl fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well as by physical methods (Pradhan et al., 2015).

5. Swelling studies

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMRimaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus was

calculated as per the following formula (Nile et al., 2014).

Swelling ratio = Weight of wet formulation / Weight of formulations

6. Determination of the drug content

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, Near infrared spectroscopy (NIRS), Microtitrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES) and also by using spectroscopy techniques (Mane and Ghurghure, 2013).

7. Percentage entrapment efficiency

Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration (Kumar and Chand, 2013).

8. *In-vitro* release studies

In vitro release studies (USP dissolution apparatus) were performed to provide the amount of the drug that is released at a definite time period. Release studies were performed by using Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus (Ali et al., 2005).

9. Powder X-Ray Diffraction

X-ray powder diffraction (Philips analytical, model-pw1710) is the predominant tool for the study of poly-crystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples were irradiated with α radiation and analyzed between 2 ºC and 60 ºC. The voltage and current used were 30KV and 30mA respectively.

10. Fourier transforms infrared analysis

Fourier transform infrared spectroscopy is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug loaded polymer formulations were obtained on FT-IR. The pellets were prepared on

KBr- press under hydraulic pressure of 150kg/cm^2; the spectra were scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature.

11. Differential scanning calorimetry (DSC)

DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25°C- 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min (Sambathkumar et al., 2012).

MATERIAL AND METHODS

Material

All the polymers, gums, reagents and chemicals were procured from various sources and were used without any purification or processing in the form they were obtained from the sources.

Methods

A. Preformulation Studies (Chaurasia, 2016)

For performing the preformulation studies of the drug, various tests of identification like physical appearance, melting point and FTIR spectroscopy were done. The solubility study of drug in various solvents, compatibility study using FTIR, partition coefficient and preparing the calibration curve of drug was also done.

a. Solubility Profile of Drug

The qualitative determination of solubility of pregabalin was performed in various solvents by adding a very small quantity of pregabalin to 1 mL of solvent in test tube. The test tube was shaken to aid in solubility of drug and the test solution was inspected visually for any undissolved particles.

b. Partition Coefficient (Hanson et al., 2019)

The partition coefficient of pregabalin was determined by using 1-octanol as oil phase (10 mL) and water as aqueous phase (10 mL) in a separating funnel. 5 mg of pregabalin was added to a mixture of both the phases and the phases were mixed by vigorous shaking in

a separating funnel. The mixture was allowed to stand overnight undisturbed to separate the phases. The water phase was withdrawn in a conical flask and then analyzed by UV spectrophotometer against blank solution and the partition coefficient was calculated by following formula.

Ko/w = Concentration of drug in 1-octanol/ Concentration of drug in water

c. Calibration curve of pregabalin (Gujral et al., 2009)

A previously reported UV spectrophotometric method was used for evaluating the pregabalin content in the samples. The calibration curve was constructed in the concentration range of 0.5-5.0 µg/mL.

d. Standard curve in distilled water

50 mg drug was dissolved in 10 mL double distilled water and the volume was made up to the mark of 50 mL using distilled water. This stock solution was diluted appropriately with the distilled water to prepare working standards of 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 µg/mL strengths. The absorbance was measured for these standards by UV visible spectrophotometer at 210 nm and calibration curves were plotted for absorbance versus concentration.

B. Formulation of gastroretentive tablets

The mucoadhesive gastroretentive tablets of pregabalin were formulated with various ratio and blends of the natural gums.

Pregabalin, chitosan, xanthan gum and gum moringa were accurately weighed and taken in a mortar as per the formula mentioned in Table 1. To the mix was added MCC and triturated for proper blending of the components. The powder blend was sifted using sieve no. 80. A presifted (sieve no. 80), accurately weighed quantity of Magnesium stearate and Talc were added to this blend and all the components were blended together to obtain the tablet blend. This blend was evaluated for powder characteristics and finally compressed as uncoated tablets with the help of a single punch tablet punching machine.

Table 1: Batch Formula for formulation of gastroretentive tablets.

	F1	F2	F3	F4	F5	F6	F7
Pregabalin (mg)	50	50	50	50	50	50	50
Chitosan (mg)	40		50		60		35
Gum Moringa (mg)	70	70	60	60	50	50	40

Gum Xanthan (mg)		40		50		60	35
MCC (mg)	70	70	70	70	70	70	70
Magnesium Stearate (mg)	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5
Total Weight (mg)	240	240	240	240	240	240	240

C. Evaluation of powder characteristics

Repose angle (θ), Bulk and Tapped density, Carr's Index, and Hausner's ratio were evaluated as the precompression parameters.

a. Angle of repose

Angle of repose was determined by the use of fixed funnel method. Accurately weighed amount of compression blend was placed funnel the height of which was fixed and the compression blend was flown through the funnel freely on to the surface such that the tip of heap touches the tip of the funnel. The averaged diameter of powder heap was measured and the angle of repose was calculated using the formula:

$$\text{Tan } \theta = h/r$$

Where, h is the height of tip of funnel; θ is the angle of repose; and r is the radius of the heap

b. Bulk and Tapped Density

Bulk density is the ratio of given mass of powder to its bulk volume. The bulk density was determined by placing the weighed compression blend into a graduated cylinder and measuring the volume (mL). Density was calculated using the formula:

$$\rho_b = M/V_b$$

Where, ρ_b is the bulk density; M is the mass of the blend and V_b is the volume occupied by the precompression blend.

Tapped density was determined by tapping the above cylinder for a 100 taps at fixed distance using tapped density apparatus. The tapped density was computed using the formula:

$$\rho_t = M/V_t$$

c. Hausner's Ratio

Hausner's ratio was calculated from the bulk and tapped density using the formula:

Hausner's Ratio = Tapped density/ Bulk density

d. Percent compressibility (Carr's Index)

Compressibility is an important measure that can be determined using the data of bulk and tapped densities. The flow ability of the granules was measured by the application of compressibility index given by the equation:

$$I = (1 - Vf/Vo)\ X\ 100$$

Where Vf = volume of the sample after tapping; V_0 = volume before tapping

In Carr's Index, the value below 15% indicates good flow properties whereas a value above 25% indicates poor flow characteristics.

D. Evaluation of gastroretentive tablets

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, thickness, weight variation, hardness, friability, swelling index, dissolution study.

a. Hardness test

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

b. Friability test

The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by the formula

$$\%\ \text{Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

c. Weight variation test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average

weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

d. Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

e. Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 10 mg of drug was dissolved in distilled water and volume was made up to 100 ml using distilled water. 10ml of the filtrate was made up to 100ml with distilled water. 10µg/ml solution was prepared from the above solution and analyzed for drug content using UV spectrophotometer at 210 nm.

f. In-vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated tablets. The dissolution media used consisted of 900 mL of 0.1 N HCl and distilled water. 5 mL of samples were collected at time points of every hour until 12 h and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 210 nm.

g. Swelling Index

One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 7.2. At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed (Qin et al., 2018). The weighing was continued for every 2 hr, till the end of 9 h. The % weight gain by the tablet was calculated by formula

$$S.I = \frac{Mt - Mo}{Mo} * 100$$

Where, S.I = swelling index, M_t = weight of tablet at the time (t) and M_0 = weight of tablet at time 0.

E. Stability Study

The formulated tablets were stored at room temperature and at 45°C in order to assess it stability. The swelling study and drug content was analyzed at the end of 3 months of storage.

CONCLUSION

The study indicate that use of chitosan, xanthan gum and gum moringa as the mucoadhesive polymers could help in achieving sustained release over a longer duration and help in reducing the dose as well as frequency of administration of the medicaments.

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