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A REVIEW ON GASTRORETENTIVE TABLETS OF GABAPENTIN

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ABSTRACT

Gabapentin was introduced in 1994 as an adjuvant antiepileptic drug. Of late, it has found applications as a broad spectrum analgesic and as a multimodal peri-operative drug. The absorption of Gabapentin is dose dependent due to a saturable transport system. It is extensively distributed in human tissues & fluids after oral administration. It does not bind to plasma proteins & is not metabolized. The elimination half-life after a single oral dose is 5-7hrs. It crosses the blood brain barrier rapidly. So the floating tablet formulations are needed for Gabapentin to prolong its duration of action, to increase its oral bioavailability and to improve patient compliance**.** Many methods are used for preparing floating tablet preparations of Gabapentin by using various grades of Hydroxypropyl methyl celluloses (HPMC K4M, K15M, K100M) at various concentrations 10%, 20% and 30%. This review article comprises of the research materialized in the field of formulation and evaluation of floating tablets of Gabapentin.

KEYWORDS: Oral Route, Gastroretentive, Floating Tablets, Gabapentin, HPMC, Antiepileptic.

1. INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration.[1] The oral route is most preferable route for administration of the drug but it may have some disadvantages like slow onset of action or slow absorption. This problem can be overcome by using alternative dosages form or administrating the drug via other routes. While we are selecting a dosage form or route for administration of drug there are some parameters should be consider like stability and bioavailability of the formulation as well as active

pharmaceutical ingredients.[2] Tablets are the most commonly and widely used dosage form. This type of drug delivery system is called conventional drug delivery system and is known to provide an immediate release of drug. Such immediate release (IR) products results in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached another dose is usually given if a floating longer therapeutic effect is desired. Conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[3]

However the oral route of administration suffers with certain drawbacks mainly short residence time of the dosage form in the GI tract, unpredictable gastric emptying and degradation of the drug due to highly reactive nature of GI contents. Gastric emptying is a complex process and makes *in vivo* performance of the drug delivery system uncertain. Formulation of floating drug delivery systems is an useful approach to avoid this variability with increased gastric retention time of the drug delivery system. Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach .This results in an increased gastric residence time and a better control of the fluctuation in plasma drug concentration.[4,5]

Gabapentin, marketed under the brand name Neurontin among others, is a medication used to treat epilepsy, neuropathic pain, and hot flashes.[6] It is recommended as a first line agent for the treatment of neuropathic pain arising from diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain.[7] The exact mechanism of action is not well understood but its analgesic efficacy & safety has been demonstrated in physiological & pathological pain. Despite its structural similarity with GABA it does not act via mechanism related to GABA.[8] However, due to its short half-life (5-7h) and low bioavailability (60%), traditional immediate-release gabapentin solid dosage forms need to be administrated three times a day. Gabapentin is preferentially absorbed in duodenum through a suitable L-amino acid transport system. So gastric retained dosage is particularly beneficial for delivery of gabapentin since

the dosage form would be able to keep the drug in the region of absorption window and show improved bioavailability by virtue of slower release rate that avoid saturation of carrier mediated transport of conventional dosages.[9,10]

The most commonly method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Hence in the present work an attempt has been made to develop prolong release matrix tablets of Gabapentin using hydrophilic matrix materials like HPMC K100, K15M and K4M.

Several gastro retentive floating formulation has been prepared for Gabapentin by different polymers and techniques. A few are described as mentioned below.

CH. Swarna Kamala Chinthala et al designed the floating tablets of Gabapentin using effervescent technology by direct compression method. Gastro retentive systems can remain in the gastric region for several hours and hence prolongs the gastric residence time of drugs. The present research work was an attempt to formulate and evaluate gastroretentive floating drug delivery system containing gabapentin in the form of tablets using polymers like HPMC K100M, HPMC K15M, Polyox WSR 303 and sodium bicarbonate as gas generating agent. The tablets were prepared by direct compression method. The tablets were evaluated for the pre and post compression parameters such as weight variation, thickness, friability, hardness, drug content, in vitro buoyancy studies and *in vitro* dissolution studies and results were within the limits. The in-vitro dissolution studies were carried out in a USP type-II apparatus in 0.1 N HCl. Among all the formulations (F1 to F9) prepared, batch F7 was the best formulation which showed buoyancy lag time 6sec and the tablet remained buoyant for > 24h. At all the strengths of the polymer tested combination of HPMC K100M and POLYOX WSR 303 (2:1) gave relatively slow release of gabapentin over 24 h when compared to other formulations. The invitro data is fitted in to different kinetic models and the best-fit was achieved with the Higuchi model. The optimized formulation F7 followed first order release kinetics followed by non fickian diffusion.[11]

Bhargavi *et.al* designed the gastroretentive controlled release matrix tablets of gabapentin by direct compression method. A controlled release system is designed to provide constant or nearly constant drug levels in plasma with reduced dose, frequency of administration and

fluctuations in plasma concentrations via slow release over an extended period of time. One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Gabapentin is an anti epileptic drug used for the treatment of epileptic seizures and in treatment of post therapeutic neuralgia. In this study controlled released Gabapentin matrix tablets were prepared by using different matrix forming polymers which include hydrophilic polymers like HPMC K15M, HPMC K100M, Xanthan gum and hydrophobic polymer like Ethylcellulose in various ratios to retard the release of drug upto 12hrs. The formulations containing the combination of hydrophilic and hydrophobic polymer combinations (HPMC K100M with Ethycellulose) and the formulations prepared with the combination of two hydrophilic polymers of synthetic and natural origin (HPMC K100M with Xanthan Gum) exhibited maximum drug release (99%) upto12hrs during in vitro dissolution studies with optimum swelling characteristics.[12]

Neha M Dembla et.al designed the gastroretentive controlled release tablets of Gabapentin by direct compression method. The objective of the present study was to develop a pharmaceutically equivalent, stable, robust, cost effective and quality improved formulation of Gabapentin controlled release tablets by using different grades of controlled release polymer. The design of dosage form was performed by choosing Hydroxypropyl Methyl Cellulose (HPMC K100MCR), Hydroxypropyl Methyl Cellulose (HPMC K15MCR), Microcrystalline Cellulose (MCC) and Di-calcium phosphate polymers as matrix builders. The drug-polymer compatibility studies were performed. Blend Uniformity was studied and accordingly the flowability was optimized for the powder blend. Tablets were prepared by direct compression with free flowing powder. The network formed by HPMC, MCC and DCP had been coupled satisfactorily with the controlled resistance, *in vitro* release and FT-IR. Mean dissolution time was also reported to compare various dissolution profiles. The formula was finalized by comparing the *in vitro* dissolution with that of the innovator SR and IR tablets. Optimized formulation of Gabapentin was formulated using 23% HPMC K100MCR and 10% of DCP. *In vitro* drug release profile was examined 98.69% within 12h. The releases of the formulation were fitting to Hixson Crowell model suggesting controlled zero order release from the formulation. The results suggested that direct compression is a suitable method to formulate controlled release Gabapentin tablets and it can perform therapeutically better than conventional immediate release dosage form.[13]

Manish R. Bhise et al formulated the HPMC based matrix tablets of Gabapentin by direct compression method. The purpose of this work was to develop extended release (ER) matrix tablets of gabapentin, an anticonvulsant drug. Te tablets were prepared by direct compression method along with hydrophilic matrix materials like HPMC K4M, HPMC K 15M and HPMC K 100M. Te blends were evaluated for bulk density, angle of repose and compressibility index. Te tablets subjected to thickness, diameter, weight variation test, drug content, hardness, friability and in vitro release studies in 0.1N HC1 solution for the initial 2h, followed by pH 6.8 phosphate bufer solutions up to 12 hours. Te drug release study revealed that matrix tablets containing HPMC K 15M and HPMC K 100M polymer exhibited more extended release than the tablets containing other polymers. Formulation F7 showed desired drug release up to 12 h. For the optimized formulation, kinetic modeling of in vitro dissolution profles revealed the drug release mechanism ranges from difusion controlled or Fickian transport to anomalous type or non-Fickian transport. Fitting the in vitro drug released data to Korsmeyer equation indicated that difusion along with erosion could be the mechanism of drug release in optimized formulation F7.[14]

M. Vikramaditya Reddy et al formulate the mucoadhesive tablets of the Gabapentin by direct compression method. The present research work was an attempt to Formulate and Evaluate Gabapentin Gastroretentive mucoadhesive tablets to prolong gastric residence time and increase drug absorption further increasing the bioavailability. The tablets were prepared by direct compression method using mucoadhesive polymers like Carbopol 934P, Sodium Carboxy Methyl Cellulose (SCMC), Sodium alginate along with other standard excipients like Microcrystalline cellulose, Magnesium stearate and Aerosil. FTIR study confirmed the absence of any drug/polymers/excipients interactions. The prepared tablets evaluated by different parameters such as Thickness, Weight variation, Hardness, Content Uniformity, Swelling Index and Mucoadhesive strength. Indigenously fabricated assembly was used to measure the Mucoadhesive strength of the Mucoadhesive tablets and goat gastric mucosa was used as a model tissue. Mucoadhesive strength increased with increasing Polymer concentrations. The tablets were also evaluated for in vitro drug release in 0.1N HCl for 12 h in USP type 2 dissolution apparatus. Among all the formulations (F-1 to F-12) prepared, batch F-4 (0.5% C-934P) gave relatively slow release of Gabapentin over 12 h when compared to other formulations. The in-vitro data is fitted in to different kinetic models and the best-fit was achieved with the Peppas model. The optimized formulation F-4 followed

Zero order release kinetics followed by non-fickian transport. Mucoadhesive tests assured the prolonged Gastroretention of tablets. It also shows no significant change in physical appearance, Drug content, Mucoadhesive strength or in-vitro dissolution pattern after storage at 45^0C at 75% RH for a period of 3 months.[15]

2. CONCLUSION

To achieve the prolong effect in epilepsy i.e. antiepileptic, the drug availability must be ensured in the body. The gastro retentive system prolongs release formulations attempted with different investigators mentioned above may be used commercially. Gabapentin gastro retentive tablets may be formulated with different polymers at various concentrations. With gastro retentive prolong release drug delivery system reduced frequency of dosing or increase effectiveness of the drug by localization at the site of action or enhanced bioavailability and uniform drug release may be achieved. Hence it also improves the patient convenience and compliance.

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