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Design And Development Of Gastro-Retentive Drug Delivery System

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Abstract: The main objective of the present study was to develop floating sustained release formulation containing 600 mg of Pregabalin for once daily therapy by using polymers like HPMC K100M, Sodium CMC, PEO. Gastroretentive Drug Delivery System improves the bioavailability and therapeutic efficiency of drug. In the preformulation FTIR study was carried out for pure drug (Pregabalin), Pregabalin and excipients. It has not shown any interaction. The prepared floating sustained release tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. The formulated sustained release matrix tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability, drug content. Compared to all formulations F6 showed the best buoyancy lag time, the buoyancy lag time for F6 was foud to be 50Sec.Total floating time of all formulations was found to be >12 hours. The formulation containing HPMC K 100M shows the higher swelling compared to that of the formulations containing PEO, Sodium CMC.

Index Terms - floating sustained release formulation, HPMC K100M, Sodium CMC, PEO, buoyancy and buoyancy lag time.

1. Introduction

Oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (80-12h), and the existence of an absorption window in the upper small intestine for several drugs.(Badoni A, 2012).

1.1 Factors Controlling Gastric Retention of Dosage Forms (Nayak AK, 2010)

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include :density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride.). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine.Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms. Effect of gender, posture and age Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.

1.2 Advantages of gastro-retentive drug delivery system (More S, 2018)

- It increases patient compliance by reducing dosing frequency
- Buoyancy increases gastric residence time
- Better therapeutic effect of short half-life drugs
- Site specific drug delivery to stomach can be achieved
- Gastric irritation can be avoided by designing sustained release.
- No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly.
- Delivery of drugs with narrow absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril,etc.
- Targeted therapy for local ailments in the upper GI tract.

1.3 Disadvantages of gastro-retentive drug delivery system (More S, 2018)

- Floating systems has limitation, that they require high levelof fluids in stomach for floating and working efficiently. So more water intake is prescribed with such dosage form.
- In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
- Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
- Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
- Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

2. Formulation of Pregabalin floating tablets:

Table 1: Quantity of Raw Materials per Tablet (In mg)

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Pregabalin	600	600	600	600	600	600	600	600	600
PEO	150	175	200	_	_	_	_	_	_
HPMC K100M	_	_	_	150	175	200	_	_	_
SodiumCMC	_	_	_	_	_	_	150	175	200
MCC	75	60	45	75	60	45	75	60	45
Lactose	30	20	10	30	20	10	30	20	10
PVP	50	50	50	50	50	50	50	50	50
Aerosil	10	10	10	10	10	10	10	10	10
Mg.stearate	10	10	10	10	10	10	10	10	10
$NaHCo_3$	25	25	25	25	25	25	25	25	25

1.5 FORMULATION PROCEDURE:

Direct compression method: These formulations are prepared by direct compression technique. The following steps were taken while preparation of Pregabalin floating tablets

1. In each formulation Pregabalin , HPMC K100M, and all ingredients weremixed and pass through 40#.
2. All the ingredients were mixed thoroughly by triturating up to 15minutes.
3. The powder mixture was lubricated with magnesium stearte and also addaerosol.
4. The tablets were prepared by using direct compression method.

3. EVALUATION OF GABPENTIN FLOATING TABLETS:

Lubricated blends of all formulations was examined and determined Angle of repose, Loss on drying, Bulk density, tapped density, Carr's index and Hausner's ratio as procedure given in preformulation section. All observations are given in results and discussion section.

EVALUATION OF POWDER CHARACTERISTICS:

Table 2 : Evaluation of powder characteristics of F1-F9 Formulations

Formulation code	Angle of repose (degree± SD)	Bulk Density (gm/ml±SD)	Tapped Density (gm/ml±SD)	Carr's index (%± SD)	Hausner ratio (%± SD)
F1	27.42±0.04	0.321±0.02	0.347±0.02	15.35±0.06	1.03±0.05
F2	28.17±0.01	0.335±0.04	0.369±0.04	16.61±0.07	1.33±0.04
F3	28.01±0.03	0.349±0.06	0.371±0.07	15.64±0.04	1.24±0.02
F4	28.57±0.07	0.317±0.04	0.327±0.06	14.46±0.01	1.23±0.06
F5	27.77±0.09	0.297±0.03	0.331±0.05	13.29±0.05	1.35±0.03
F6	24.61±0.06	0.281±0.01	0.335±0.01	17.35±0.03	1.25±0.01
F7	27.16±0.03	0.287±0.04	0.367±0.03	15.46±0.07	1.30±0.03
F8	28.11±0.09	0.317±0.05	0.376±0.02	16.61±0.04	1.29±0.05
F9	25.05±0.02	0.330±0.06	0.369±0.04	12.85±0.09	1.31±0.00

Table 3: Physical Evaluation of formulated tablets

Formulation code	Weight variation (n=20) (mg ± SD)	Hardness (kg/cm^2±SD)	Friability(%)	Drug content (%± SD)	Thickness (%± SD)
F1	962±0.29	6.7±0.1	0.69	98.13±0.04	5.2±0.007
F2	961±0.67	6.6±0.2	0.67	99.19±0.01	5.3±0.006
F3	959±0.45	7.1±0.3	0.74	99.29±0.12	5.2±0.011
F4	961±0.71	6.8±0.5	0.71	98.19±0.09	5.3±0.008
F5	958±0.15	7.3±0.2	0.65	99.17±0.07	5.2±0.009
F6	962±0.31	6.9±0.4	0.63	97.61±0.03	5.2±0.013
F7	959±0.04	6.6±0.3	0.76	98.13±0.17	5.3±0.004
F8	958±0.71	7.4±0.3	0.70	96.11±0.14	5.2±0.012
F9	961±0.52	7.5±0.5	0.68	98.21±0.05	5.3±0.05

Table : 4 Floating time of Pregabalin tablets

Formulation Code	Lag time (seconds)	Total floating Time (hours)
F1	69	>12
F2	56	>12
F3	60	>12
F4	70	>12
F5	59	>12
F6	50	>12
F7	65	>12
F8	74	>12
F9	68	>12

Table 5: Percentage swelling index of formulated tablets

Formulation Code	Percentage Swelling index				
	Time (hours)				
	1	**2**	**3**	**4**	**5**
F1	30.06	41.68	59.78	71.56	82.64
F2	32.45	46.65	62.54	78.58	89.09
F3	29.26	49.64	63.24	86.35	92.64
F4	25.98	42.82	64.68	79.04	88.97
F5	27.57	54.65	68.12	80.5	92.36
F6	29.34	57.68	73.56	84.75	97.51
F7	28.00	41.76	50.99	71.24	86.29
F8	30.11	44.38	58.49	77.63	90.23
F9	26.16	49.25	64.21	81.87	94.19

Table 6: *In-vitro* drug release study of formulated sustained releaseformulations

TIME (hours)	CUMULATIVE PERCENT DRUG RELEASE (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	33.25	27.46	21.31	35.33	24.96	21.32	30.66	25.57	24.82
2	50.68	44.74	32.64	51.24	46.76	32.17	48.45	49.68	38.95
4	75.62	62.10	58.21	79.11	59.47	59.09	72.04	65.49	52.14
6	82.51	84.45	64.54	92.21	86.88	66.70	89.34	78.64	76.31
8	98.25	93.48	78.90	98.98	92.36	85.68	99.69	91.45	88.49
10	-	98.38	84.41	-	99.23	94.58	-	99.10	92.62
12	-	-	99.08	-	-	99.96	-	-	98.48

4. CONCLUSION

The main objective of the present study was to develop floating sustained release formulation containing 600 mg of gabapenin for once daily therapy by using polymers like HPMC K100M, Sodium CMC, PEO. Gastroretentive Drug Delivery System improves the bioavailability and therapeutic efficiency of drug. n the preformulation FTIR study was carried out for pure drug (Pregabalin), Pregabalin and excipients. It has not shown any interaction.

The formulations were prepared by direct compression method . The powders of all batches showed good flow properties evident from the results shown in table-27. The angle of repose values were ranged from 27..42±0.06to 28.11±0.09. The results were found to be below 30; hence they have good flow ability. The Carr's index value ranged from 12.85±0.09 to 17.35±0.03 and Hausner's ratio value ranged from 1.03±0.05to 1.29±0.05 hence they have good flow and free flow ability.
The prepared floating sustained release tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. The formulated sustained release matrix tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability, drug content. The weight variation of tablets was uniform in all formulations and ranged from 958±0.151to 962±0.29. The hardness of the prepared tablets was ranged from 6.6±0.2 to 7.5±0.3, friability values were ranged from 0.63 to 0.76. Drug content of tablets was ranged from 98.11±0.03 to 99.91±0.14, thickness of tablets was uniform and values are ranged from 5.2±0.002 to 5.3±0.006. The buoyancy lag time of all the formulations were ranged from 50 Sec to 70 Sec. Compared to all formulations F6 showed the best buoyancy lag time, the buoyancy lag time for F6 was foud to be 50Sec.Total floating time of all formulations was found to be >12 hours. The formulation containing HPMC K 100M shows the higher swelling compared to that of the formulations containing PEO, Sodium CMC.

The prepared tablets were then subjected to dissolution test for evaluating the invitro drug release.The dissolution studies were carried out in 0.1N Hcl in USP II appatarus at 37±0.5oC. The results of the dissolution studies indicated that the polymer concentration is having a substantial effect on the drug release from the tablets. Formulation F6 gave better sustained drug release and floating properties in comparision to the other formulations. This formulation took 50Sec to become buoyant.

The kinetic study was carried out for F6 formulation which showed that the drug release follows zero order kinetics.
The stability studies were carried out for F6 formulation at 40oC ± 2oC / 75% RH
± 5% for 3months. Data revelead that there was no considerable difference.

From the above study, it can be concluded that F6 is the optimized formulation which has shown better buoyancy time 50 Sec and drug release 99.85% . However, further in vivo studies can be carried out to support the results.

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