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FORMULATION, DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE MATRIX TABLETS OF USING NATURAL POLYMERS FOR TREATMENT OF DEPRESSION

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ABSTRACT

The present study aimed to formulate, develop, and evaluate gastroretentive matrix tablets of trazodone hydrochloride using natural polymers for the effective treatment of depression. Trazodone hydrochloride is an antidepressant drug with a relatively short half-life, which requires frequent dosing. Therefore, the development of a gastroretentive drug delivery system was considered to enhance gastric residence time and provide sustained drug release. The matrix tablets were prepared by the direct compression method using different concentrations of natural polymers. The prepared powder blends were evaluated for pre-compression parameters such as bulk density, tapped density, compressibility index, and Hausner's ratio to determine their flow properties. The compressed tablets were further evaluated for post-compression parameters including thickness, hardness, weight variation, friability, and drug content. The swelling behavior and bioadhesion strength of the formulations were also determined to assess their gastroretentive potential. *In-vitro* drug release studies were performed to evaluate the release profile of trazodone hydrochloride from the matrix tablets. The results showed that all formulations exhibited acceptable physicochemical properties. Among the formulations, F5 showed higher swelling index, better bioadhesion strength, and sustained drug release up to 12 hours. The drug release kinetics indicated that the release mechanism followed the Korsmeyer–Peppas model, suggesting diffusion-controlled drug release. Thus, the developed gastroretentive matrix tablets of trazodone hydrochloride using natural polymers could be considered a promising approach for sustained drug delivery and improved therapeutic efficacy in the management of depression.

Keywords: Trazodone hydrochloride, Gastroretentive drug delivery system, Matrix tablets, Natural polymers, Sustained release, Depression.

INTRODUCTION

Depression is a common mental health disorder characterized by persistent sadness, loss of interest in daily activities, fatigue, and impaired cognitive function (Katon, 2006). It significantly affects an individual's quality of life and is considered one of the leading causes of disability worldwide. The condition may arise due to various factors including genetic predisposition, biochemical imbalance, psychological stress, and environmental influences. Effective management of depression generally involves pharmacological therapy with antidepressant

drugs that help restore neurotransmitter balance in the brain (Simon and Von Korff, 2007).

Among the various antidepressant medications, Trazodone hydrochloride is widely used for the treatment of major depressive disorder. Trazodone hydrochloride belongs to the class of serotonin antagonist and reuptake inhibitors (SARIs) (Wen *et al.*, 2008). It exerts its therapeutic effect by inhibiting serotonin reuptake and antagonizing certain serotonin receptors, thereby increasing serotonin availability in the central nervous system. Although trazodone is effective in treating depression and associated insomnia, it has a relatively short biological half-life, which requires frequent dosing to maintain therapeutic drug levels (Jaffer *et al.*, 2017).

To overcome these limitations, novel drug delivery systems such as gastroretentive drug delivery systems (GRDDS) have been developed. Gastroretentive systems are designed to prolong the residence time of dosage forms in the stomach, thereby enhancing drug absorption and improving bioavailability (Garg and Sharma, 2003). These systems are particularly useful for drugs that are primarily absorbed in the stomach or upper part of the small intestine. Floating drug delivery systems, a type of gastroretentive system, remain buoyant in the gastric fluid for an extended period and allow the drug to be released slowly at the desired rate (Streubel *et al.,* 2003).

Matrix tablets are commonly used in controlled drug delivery systems because they provide sustained and controlled drug release over a prolonged period (Basanta *et al.*, 2016). In matrix tablets, the drug is uniformly dispersed within a polymer matrix, which controls the drug release through mechanisms such as diffusion, swelling, and erosion. The use of natural polymers in matrix formulations has gained considerable attention due to their biocompatibility, biodegradability, non-toxicity, and cost-effectiveness. Natural polymers such as guar gum, xanthan gum, chitosan, and sodium alginate have been widely investigated for controlled drug delivery applications.

The development of gastroretentive matrix tablets of trazodone hydrochloride using natural polymers offers several advantages including prolonged gastric residence time, reduced dosing frequency, improved patient compliance, and enhanced therapeutic efficacy (Gambhire *et al.,* 2007). The formulated tablets are generally evaluated for various pre-compression parameters such as bulk density, tapped density, Carr's index, and Hausner's ratio, as well as post-compression parameters including hardness, friability, weight variation, drug content, and *in-vitro* drug release studies.

Therefore, the formulation and evaluation of gastroretentive matrix tablets of Trazodone hydrochloride using natural polymers represents a promising approach to achieve sustained drug release and improve the therapeutic management of depression.

MATERIALS AND METHODS

Materials

Trazodone hydrochloride was used as the model drug in the present study. Natural polymers such as guar gum and xanthan gum were employed as matrix-forming agents to control the drug release. Other excipients including microcrystalline cellulose (MCC) were used as diluent, magnesium stearate as

lubricant, and talc as glidant to improve the flow properties and compression characteristics of the powder blend. All chemicals and reagents used in the study were of analytical grade and were used as received without further purification.

Methods

Method for preparation of Trazodone hydrochloride mucoadhesive matrix tablet

Direct compression was taken after to manufacture the mucoadhesive tablets of Trazodone hydrochloride (Patil *et al.,* 2011). Six different formulations (F1, F2, F3, F4, F5, and F6) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in Table no. 1 and all the definition were utilized for encourage assessments parameters.

Evaluation of powder blend

There are many formulations and process variables involved in mixing step and all these can affect characteristics of blend produced (Cooper and gunn, 1986; Shah and Rampadhan 1997). Angle of repose, bulk density, true density and percent compressibility index have been measured which are given in table.

Bulk density

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure:-

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml gm/ml, by the formula:

Bulk density = Bulk Mass/ Bulk Volume

Compressibility index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. It can be calculated as per given formula:

$$C.I. = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio:

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes (Hadjiioannou *et al.,* 1993):

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (--).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the

powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 246.0 nm using 0.1 N HCl blank.

Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach).

Friability

The friability of sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Swelling Index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and 0.1 N HCl was used as medium, and the temperature was maintained at 37 ± 0.5°C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W_2) (Lalla and Gurnancy, 2002). Percent hydration (swelling index) was calculated as shown in Table 8.8 using the following formula:

Swelling index = $(W_2 - W_1) \times 100/W_2$

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet.

***In vitro* mucoadhesive Strength**

The mucoadhesive strength of the prepared tablets was determined using a modified physical balance method. The experimental setup consisted of a modified double-beam physical balance in which the right pan of the balance was replaced by a glass assembly used to hold the tablet and mucosal membrane.

In this method, a piece of freshly excised mucosal tissue was fixed onto a glass slide using an appropriate adhesive. The tablet was attached to another glass slide, which was connected to the balance through a suitable support. The mucosal tissue was kept moist with phosphate buffer solution to simulate physiological conditions. The tablet was then brought into contact with the mucosal surface by applying slight pressure for a fixed period of time to ensure proper adhesion.

After the contact time, weights were gradually added to the opposite pan of the balance until the tablet detached from the mucosal surface. The minimum weight required to detach the tablet from the mucosal membrane was recorded as the mucoadhesive strength. This method provides an estimation of the adhesive force between the tablet and mucosal surface, which indicates the potential of the formulation to remain attached to the gastric mucosa for a prolonged period.

Determination of mucoadhesive strength

The working of a double beam physical balance formed the basis of the bioadhesion test assembly. The left pan was removed and hung with a stainless steel chain. A Teflon block with 1.5 in height and 1.5 in diameter was hung with the stainless steel chain to

balance the weight of the other pan. The height of the total set up was adjusted to accommodate a glass container or beaker below it leaving a head space of about 0.5 cm in between. Block of 2 in height and 1.5 in diameter was kept inside the glass vessel, which was then positioned below the top hung Teflon block. Suitable weights were added on the right pan to balance the beam of the balance.

The porcine gastric mucosa was attached with the mucosal side upward onto the lower Teflon block which was then placed in the glass vessel. Sufficient simulated gastric fluid was filled into the beaker so that the surface of the fluid just touches the mucosal surface to Teflon block. A tablet was fixed to the bottom portion of the cylindrical shaped base with 'feviquick' glue. The string with tablet was hung in such a way that the tablet was just in contact with the surface of the mucosal side of pig stomach when the balance was in a balanced position. The balance was left in a balanced position for fixed time of 5 minutes and then slowly weights were increased on the right pan until the tablet detaches from the surface of the intestinal mucosa. The weights on right side pan gave the mucoadhesive strength of the tablet in grams. From mucoadhesive strength, the bioadhesion force was calculated per unit area of the tablet as follows:

$$F=\frac{Ww \times G}{1000 \times A}$$

Where F is the bioadhesion force ($kg/m/s^2$), Ww is the mass applied (g), g is the acceleration due to gravity (cm/s^2) and A is the surface area of the patch (cm^2).

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1 N HCl was set into the dissolution flask maintaining the temperature of 37±0.5ºC and rpm of 75. One Trazodone hydrochloridetablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 246.0 nm using spectroscopy (Shinkar *et al.,* 2012; Derle *et al.,* 2009; Bramhankar and Jaiswal, 2008; Costa and Lobo, 2001; Korsemeyer *et al.,* 1983).

RESULTS AND DISCUSSION

The powder blends of trazodone hydrochloride prepared for matrix tablet formulation were evaluated for pre-compression parameters such as bulk density, tapped density, compressibility index, and Hausner's ratio to determine their flow properties prior to compression. The results are presented in Table 2. The bulk density of the formulations ranged from 0.344 to 0.385 g/ml, while the tapped density ranged from 0.458 to 0.496 g/ml. The compressibility index values were found between 22.37% and 24.89%, and the Hausner ratio ranged from 1.288 to 1.331. These values indicate acceptable flow properties of the powder blends, suggesting that the mixtures were suitable for direct compression during tablet formulation.

The prepared matrix tablets were evaluated for post-compression parameters including thickness, hardness, weight variation, friability, and drug content, and the results are summarized in Table 3.

The thickness of the tablets ranged from 2.3 ± 0.3 mm to 2.5 ± 0.2 mm, indicating uniform tablet dimensions. The hardness values were between 5.6 ± 0.5 and 5.9 ± 0.3 kg/cm², demonstrating adequate mechanical strength of the tablets. The friability values were found to be less than 1% for all formulations, confirming good mechanical resistance to abrasion. The weight variation of the tablets ranged from 243 ± 9 mg to 265 ± 3 mg, which falls within acceptable pharmacopeial limits. The drug content was found between 96.65 ± 0.23% and 99.12 ± 0.25%, indicating uniform distribution of trazodone hydrochloride within the matrix tablets.

The swelling behavior of the matrix tablets was evaluated to understand the hydration and swelling characteristics of the polymer matrix, and the results are shown in Table 4. The swelling index increased progressively with time for all formulations, indicating the ability of the natural polymers to absorb water and form a gel layer around the tablet. Among all formulations, F5 exhibited the highest swelling index, reaching 96.65% at 12 hours. This higher swelling behavior indicates better matrix formation and controlled drug release capability of the polymer system used in formulation F5.

The bioadhesion strength of the prepared formulations was determined to evaluate their ability to adhere to the gastric mucosa, which contributes to prolonged gastric retention. The results are presented in Table 5. The force of adhesion ranged from 0.55 ± 0.3 to 0.79 ± 0.2 among all formulations. The highest bioadhesion strength was observed in formulation F5 (0.79 ± 0.2), indicating stronger adhesion to the gastric mucosal surface and enhanced gastroretentive potential.

The in-vitro drug release profile of the optimized formulation F5 was studied and the results are presented in Table 6. The formulation showed an initial release of 28.89% drug within 0.5 hours followed by a gradual and sustained release pattern over 12 hours. The cumulative drug release reached 99.78% at the end of 12 hours. This controlled release behavior suggests that the polymer matrix effectively regulated the release of trazodone hydrochloride, ensuring prolonged therapeutic action.

To understand the mechanism of drug release, the dissolution data of the optimized formulation F5 were fitted into various kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The regression analysis results are shown in Table 7. The highest correlation coefficient (r^2 = 0.9834) was observed for the Korsmeyer–Peppas model, followed by the Higuchi model (r^2 = 0.9579). This indicates that the drug release from the matrix tablet followed diffusion-controlled release with polymer relaxation mechanisms. The results confirm that the natural polymer-based matrix system successfully controlled the release of trazodone hydrochloride over an extended period.

Table 1: Various formulations of Trazodone hydrochloride matrix tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6
Trazodone hydrochloride	25	25	25	25	25	25
Sodium alginate	40	60	-	-	20	30
Gum tragacanth	-	-	40	60	20	30
Gaur gum	10	20	10	20	10	20
MCC	155	125	155	125	145	125
Talc	10	10	10	10	10	10
Mg Stearate	10	10	10	10	10	10
Total Weight	250	250	250	250	240	250

Table 2: Result of pre-compression properties of Trazodone hydrochloride

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.385	0.496	22.379	1.288
F2	0.365	0.475	23.158	1.301
F3	0.374	0.482	22.407	1.289
F4	0.365	0.476	23.319	1.304
F5	0.344	0.458	24.891	1.331
F6	0.358	0.463	22.678	1.293

Table 3: Results of post compression properties of Trazodone hydrochloride matrix tablets

Formulation code	Thickness*(mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	2.4±0.2	5.9±0.3	255±5	0.658±0.015	98.78±0.12
F2	2.5±0.1	5.8±0.2	245±5	0.745±0.023	98.65±0.15
F3	2.3±0.3	5.6±0.5	265±3	0.632±0.045	98.78±0.25
F4	2.4±0.2	5.8±0.6	243±9	0.775±0.023	96.65±0.23
F5	2.5±0.2	5.7±0.4	247±8	0.698±0.032	99.12±0.25
F6	2.4±0.1	5.8±0.2	252±5	0.569±0.015	99.05±0.14

Table 4: Results of Swelling Index of Trazodone hydrochloride matrix tablets

Formulation Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	18.85	43.32	73.32	88.98
F2	25.65	48.88	76.65	96.65
F3	23.24	46.65	71.15	76.65
F4	27.74	50.22	76.65	82.32
F5	29.98	55.65	88.98	96.65
F6	25.45	50.14	70.23	86.65

Table 5: Results of determination of bioadhesion strength

S. No.	Formulation Code	Force of Adhesion
1.	F1	0.55±0.3
2.	F2	0.62±0.2
3.	F3	0.78±0.5
4.	F4	0.68±0.3
5.	F5	0.79±0.2
6.	F6	0.69±0.2

Table 6: *In-vitro* drug release data for optimized formulation F5

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	28.89	1.461	71.11	1.852
1	1	0	36.65	1.564	63.35	1.802
1.5	1.225	0.176	45.63	1.659	54.37	1.735
2	1.414	0.301	51.78	1.714	48.22	1.683
3	1.732	0.477	66.85	1.825	33.15	1.520
4	2	0.602	72.32	1.859	27.68	1.442
6	2.449	0.778	83.32	1.921	16.68	1.222
8	2.828	0.903	98.85	1.995	1.15	0.061
12	3.464	1.079	99.78	1.999	0.22	-0.658

Table 7: Regression analysis data of Trazodone hydrochloride matrix tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
F5	0.841	0.9411	0.9579	0.9834

CONCLUSION

The present study successfully formulated and evaluated gastroretentive matrix tablets of Trazodone Hydrochloride using natural polymers. The prepared formulations showed satisfactory pre-compression and post-compression characteristics, indicating good flow properties and acceptable tablet quality. The swelling studies and mucoadhesive strength results demonstrated the ability of the tablets to retain in the gastric environment for a prolonged period. *In-vitro* drug release studies revealed sustained drug release up to 12 hours. Among all formulations, F5 showed the best performance in terms of swelling index, bioadhesion strength, and controlled drug release. Therefore, the developed gastroretentive matrix tablet formulation could be considered a promising approach for prolonged drug delivery and improved therapeutic effectiveness in the treatment of depression.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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