Design and evaluation of domperidone once daily sustained release matrix tablets

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Abstract

Domperidone sustained release tablets were formulated as matrix tablet employing different hydrophilic and hydrophobic polymers in a different ratio, and were calculated for release kinetics and mechanism. The aim of present study is to investigate the possibility of obtaining prolonged, relatively constant effective level of Domperidone from matrix tablets using different polymers such as MethocelK100 M, K15M, K4M, Eudragit RS100and RL30D, Xanthan gum, Ethyl cellulose, which gives sustained release throughout 24 hrs from the formulations.

Key words: Domperidone; Sustained release; Matrix tablets.

1. Introduction

Oral drug delivery system is an effective system known for several decades as the most widely used route of administration among all the routes, which has been employed for the systemic delivery of drug via various dosage forms (Akila et al ., 2006; Azarmi et al ., 2002; Behl, 2005; Vyas and Roop Khar, 2002). Sustained release dosage form is a one of the method to release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ

In Oral Conventional dosage form has to be administered several times to produce therapeutic efficacy, but it yields fluctuation of drug in plasma level. Drug concentration can be controlled within the narrow therapeutic range by the use of sustained release systems, which will minimize the side effects (Haririan, 2001; Helena amaral, 2001; Jaber emamil, 2004; Parakar, 2004). Sustained release formulation may be economical, because of the average cost of treatment over an extended period.

The designing of sustained release dosage form is to reduce the frequency of the dosing, effectiveness, reducing the dose required and providing the uniform drug delivery on the site of action (Paol Giunchedi, 2000). The aim of present studying of Domperidone (Raghuram Reddy, 2000) sustained release is to maintains constant drug plasma level, more effective with economic.

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2. Materials and Methods

2.1. Chemicals and Reagents

Domperidone was obtained as gift sample (Amcure Chemicals), Ethyl cellulose and Lactose (Feicheng Ruitai fine chemicals, China),Eudragit (RS100, RL30D), Xanthan gum(Rohm Pharma, Germany),Hydroxyl propyl methyl cellulose, Methocel ,Titanium dioxide, Methylene chloride (Samsung, South Korea),Polyvinyl pyrolidine(PVPK30), Polyethylene glycol (4000) (Nan hang Industrial CoLtd,China), ,Magnesium stearate (Mittal Polymers, Bombay), Isopropyl alcohol(M/S National agencies, Bombay).

2.2 Preparation of Domperidone Sustained Release Tablets

Domperidone and polymer were passed through 60 (#) mesh and the excipients were passed through sieve 40(#) mesh. It is show in table: 1 Binding solution was prepared by dissolving povidone K30 in the granulating agent and it is sonicated for 5 mins to form clear solution. Then the active ingredient were mixed with excipients and polymer in a polybag, Transferred into a tub and slowly added the binding solution with constant mixing until a coherent mass was found. Then the Passed coherent

mass passed through sieve12 (#) mesh to produce granules. Granules were dried in a tray dryer at 50Úc for 1 hr. And the dried granules passed through 16 (#) mesh. Lubricated granules by using the lubricating agents, which was previously passed through sieve60 (#) mesh. Then lubricated granules were compressed by using 6.35mm size punch on the 16 station Minipress punching machine.

2.3. Evaluation of Granules

After preparation the granules were evaluated by some official method to determine the characters of granules. Bulk densities, Tap density, Compressibility index, Hausner ratio, Angle of repose, Loss on drying tests were done (Raghuram Reddy, 2000). The result was shown in table 2.

2.4. Evaluation of Tablets

Compressed Sustained release tablets were evaluated for following official and unofficial tests such as Weigh Variation, Hardness Test, Thickness, Friability Test, Drug content test (Raghuram Reddy, 2000). The result was shown in table 3.

2.5. Drug Content of Domperidone by HPLC

20 mg of Domperidone were dissolved 2ml of 1M hydrochloric acid and about 60ml of diluents (water 50:Acetonitrile 50:1ml Diethyl amine) the drug containg samples solution were analyzed by using HPLC (Shimadzu Corporation. Japan) at 286 nm.

2.6. In vitro release study

The invitro dissolution studies of Domperidone tables were carried out in USPXXIII Apparatus (basket method) using 900ml 0.1 N Hydrochloric acid as the acidic medium and phosphate buffer (pH 6.8) as alkaline medium at 100 rpm at 37º ±1ºC used. 1 ml sample was withdrawn at predetermined interval of 24 hrs, and filtered through 0.45 μm using a membrane filter, dilute the sample solutions with appropriate buffers respectively, it was analyzed by using HPLC (Shimadzu Corporation. Japan) at 286 nm. Drug release profile is show in figure 1.

3. Results and discussion

The prepared sustained release tablets of Domperidone and its granules showing aggregation of component particles and bonds with definite strength. The granules of Domperidone were evaluated in the following parameters such as Angle of repose, Bulk density; Compressibility index and Hauser's ratio, drug content (Table2).the result of angle of repose (< 30) indicate good flow properties of granules. This was further supported by lower compressibility index (table 2).in bulk density; the granules were prepared by using Isopropyl alcohol as a granulating agents (table2).the weight of granules shows uniform drug content in all formulation. The decided compressed tablets of Domperidone were evaluated by weight variations, drug content, friability, hardness and thickness (T1toT9).No significant difference was observed in the weight of individual tablet from the average weight. Tablet weight and hardness (4.0-4.6 kg/cm2) showed within I.P limit. The uniformity of content that tablets of all batches complies within B.P limit. The percentage friability of tablets was less then 1% indicates ability of tablet to withstand shocks.

Here in trail (T1) Methocel K100m containing drugs shows high initial burst of 35.73% and attained 100.55 releases within 29 hours. Methocel K100m does not shows drug release upto 24 hrs. Trail (T2) with MethocelK15m containing shows faster release than Methocel K100m, but release pattern was within 12 hrs. Trail (T3) with MethocelK4m containing drug shows initial burst of 34.83% and attained complete release within12 hrs. Trail (T4) with Eudragit RS100 release profile shows 20 hrs retardation. In trail (T5) Eudragit RL30D used as a polymer showing the release of 20 hours. According to trail (T6) Methocel K15m and Ethyl cellulose in the ratio of 1:1, also shows the release pattern upto 20 hrs. In trail (T7) hydrophilic natural polymer of Xanthan gum was used and it shows release whole drug within 12 hrs. In trail (T8) we used Methocel K100m and Ethyl cellulose in the ratio of 2:1 also shows complete drug release within 20 hrs.

Finally in trail (T9) Methocel K100m and Ethyl cellulose in the ratio of 1:1 were prepared and release profile showed that the initial bust 34.23% and showly attained 98.36% of drug release upto 24 hrs steadily. Here Methocel K100m is used as hydrophilic polymer and ethyl cellulose as insoluble matrix former. Methocel K100m has absorbing water and it swell and ethyl cellulose helps in retarding the drug molecules from polymer matrix, hence it allows the water to diffuse into the matrix and slowly erode the same to dissolve the drug.

From the above discussion, trail (T9) was indicated (Table 4) and subjected to kinetic assessment, the data were plotted according to first order release, it shows R^2 =0.9727 to 0.9898, and suggested that the rate of drug release as follows the first order. According to the Higuchi's kinetic equation the R^2 =0.9483 to 0.9954. Indicates sustained release mechanism of diffusion. The mentioned dissolution data was subjected to Kersey mere's Pappas equation was shows n value between 0.3920 to 0.69, which indicate the Flikian release mechanism. The passed final formulation of Domperidone sustained release tablet was subjected to stability study under varies storage conditions for period of one month.

4. Conclusion

Result of present study demonstrate that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained release matrix tablets of Domperidone, based on the result, it is clearly evident that multiple unit dosage forms work better than single unit dosage forms.

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Table: 1 Formulation trail batches

Ingredients mg/tablet	Formulation Nos.								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
Drug	32	32	32	32	32	32	32	32	32
Methocel K100M	80	-	-	-	-	-	-	55	40
Ethyl Cellulose	-	-	-	-	-	40	-	25	40
Methocel K15M	-	80	-	-	-	40	-	-	-
Methocel K4M	-	-	80	-	-	-	-	-	-
Eudragit RS 100	-	-	-	80	-	-	-	-	-
Eudragit RL 30D	-	-	-	-	80	-	-	-	-
Xanthan gum	-	-	-	-	-	-	80	-	-
PVP K30	6	6	6	6	6	6	6	6	6
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg.Sterate.	2	2	2	2	2	2	2	2	2

Table 2: Characterization of trial blends

Trail. No.	Bulk density	Tapped density	Loss on Drying	Compressibility Index	Hausner Ratio	Angle of Repose+
T1	0.506	0.58	2.00%	12.75	1.14	24.50°
T2	0.49	0.555	1.80%	11.71	1.13	21.20°
T3	0.488	0.51	2.40%	13.08	0.63	23.42°
T4	0.424	0.486	1.20%	12.75	1.14	25.15°
T5	0.522	0.581	0.90%	10.15	1.11	30.06°
T6	0.502	0.561	1.40%	10.51	1.11	24.85°
T7	0.449	0.501	1.70%	10.37	1.12	25.26°
T8	0.491	0.56	1.60%	12.32	1.14	27.54°
T9	0.524	0.586	1.40%	10.58	1.11	28.44°

Table 3: Physical parameters of tablets (T1-T9)

Trail. No.	Weight variation (mg)*	Diameter (mm)*	Thickness (mm)*	Hardness (kg/cm2)	Friability (%)	Drug content (%)
T1	126 ±2.15	6.08±0.03	3.88 ±0.03	4.0±0.20	0.48±0.2	98.1
T2	129 ±3.14	6.05±0.02	3.79 ±0.08	4.2±0.02	0.52±0.3	97.55
T3	122 ±1.18	6.08±0.01	3.83 ±0.07	4.6±0.03	0.58±0.2	98.9
T4	128 ±1.68	6.05±0.04	3.81 ±0.06	4.0±0.02	0.48±0.4	89.9
T5	126 ±4.45	6.07±0.03	3.80 ±0.04	4.1±0.05	0.54±0.2	91.0
T6	130 ±3.01	6.08±0.04	3.79 ±0.07	4.5±0.06	0.49±0.4	95.36
T7	125 ±1.97	6.09±0.02	3.84 ±0.08	4.6±0.05	0.51±0.2	84.23
T8	126 ±2.23	6.05±0.03	3.83 ±0.09	4.0±0.06	0.52±0.3	96.80
T9	122 ±1.84	6.06±0.04	3.83 ±0.03	4.6±0.02	0.48±0.2	98.90

*Each value represents the mean ± standard deviation (n = 10)

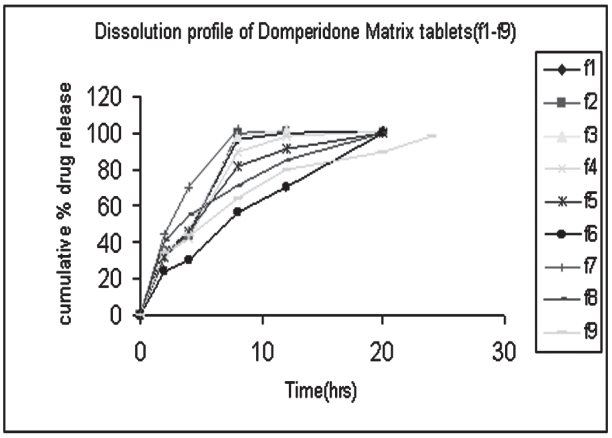
Table: 4

Drug release kinetics and correlation coefficient (R^2) of invitro dissolution release

Trail code	Drug release kinetics, correlation coefficient(R^2)			Release exponent(n)
	First order	Higuchi	Korseymere's	
T1	0.9610	0.9748	0.9835	0.50
T2	0.9101	0.9723	0.9843	0.69
T3	0.9090	0.9832	0.9853	0.64
T4	0.9415	0.9842	0.9807	0.54
T5	0.9462	0.9897	0.9845	0.52
T6	0.9863	0.9876	0.9824	0.64
T7	0.9612	0.9889	0.9908	0.61
T8	0.9421	0.9954	0.9974	0.69
T9	0.9898	0.9968	0.9979	0.54

Figure No: 1

Comparative Dissolution Profile of Batch T1 to T9 in 0.1N Hydrochloric acid & pH 6.8 phosphate buffer



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