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Original Article

Design and Evaluation of Fast Dissolving Tablets of Domperidone using Cationic Exchange Resin

Dasari Nirmala[1, *], Vidyavathi Maravajhala[2]

[1] Department of pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, and Secunderabad -500100 affiliated to Osmania University, India

[2] Institute of pharmaceutical technology, Sri Padmavathi Mahila Visvavidalayam (women's university) Tirupathi-517502, India.

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ABSTRACT

Present research work was aimed at design and evaluation of fast dissolving tablets of domperidone using super disintegrant like cross povidone ,cross carmellose sodium, sodium starch glycolate and indion 414 with various concentration of 2.5%.5% and 7.5%by direct compression method. ATR spectra shown that there are no polymer and drug interactions. The prepared tablets were evaluated for various post compression parameters like hardness, weight variation, friability, content uniformity, wetting time and water absorption ratio. The values of all parameter were within pharmacopoeial limits .Among all the formulations F12 (7.5% of indion 414) as shown 10 seconds disintegration time. *In vitro* drug release studies shows that 100.1% drug release within 20 minutes, Hence this formulation was considered as the best formulation, and its Short term stability studies were conducted at 40±2°/75%±5% RH up to 3 months it was found that *in vitro* disintegration time and drug release were not changed during stability studies.

Key words: fast dissolving tablets, domperidone, direct compression, indion 414, cationic exchange resin

1. INTRODUCTION

Oral route of administration is the preferred route for administration of various drugs. Recent developments in the pharmaceutical technology have prompted scientist to develop fast dissolving tablets (FDT) for improving patient compliance and convenience. FDT are solid unit dosage forms containing medicinal

Corresponding author *
Dasari Nirmala
Department of Pharmaceutics,
Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, and Secunderabad -500100 affiliated to Osmania University,India
Email: dasarinirmala1980@gmail.com

substances which disintegrate rapidly, usually within matter of seconds, when placed upon the tongue. FDT provide an advantage, particularly for pediatric, geriatric and bed ridden patients who have difficulty in swallowing conventional tablets. Domperidone is a peripheral dopamine (D_2) and (D_3) receptor antagonist [1, 2]. It provides relief from nausea and vomiting by blocking receptors at the chemoreceptor trigger zone. It does not readily cross the blood brain barrier. Domperidone is, therefore more advantageous than any other anti emetic drugs. As per BCS, domperidone is class II drug with poor solubility and erratic absorption in the stomach and possesses several dissolution problems [3]. In the present study an attempt was made to prepare fast dissolving tablets of domperidone by using different super disintegrants to reduce dissolution problems. FDT of domperidone were prepared using superdisintegrants like cross carmellose sodium (CCS), sodium starch glycolate (SSG) and Indion 414, a cationic exchange resin. Among which it is high molecular weight polymer, having remarkable swelling tendency. It is not absorbed by body tissues and is totally safe for human consumption [4].

2. MATERIALS AND METHODS

Materials:

Domperidone gift sample from Vignesh life sciences pvt.ltd Hyderabad. Indion414 purchased from Balagi drugs Gujarat, cross povidone, cross caramellose sodium, sodium starch glycolate, microcrystalline cellulose, mannitol, magnesium stearate and aerosil were obtained from S.D fine chemicals Mumbai.

Methods:

Attenuated total reflectance spectroscopy (brucker): To find the physical and chemical interactions or compatability between drug and excipients. Attenuated total reflectance spectra of physical mixture drug and excipients were recorded using ATR instrument.

Preparation of Domperidone fast dissolving tablets:

Direct compression [5, 6]:

Totally, 12 formulations of (F1 to F12) Domperidone FDT were prepared. All the materials were passed through 60#screens prior to mixing. Domperidone, cross povidone (F1-F3), cross caramellose sodium (F4-F6), sodium starch glycolate (F7-F9) and Indion (F10-F12), micro crystalline cellulose, mannitol, stearic acid, and aerosil were well mixed. All materials were directly compressible so this uniformly mixed blend was compressed into tablets using concave face round tooling on a tablet punching machine (REMEK MINIPRESS-IIMT). According to composition shown in table 1.

Table 1: Formulation of domperidone fast dissolving tablets

Ingredients(mg)	F1	F2	F3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
Domperidone	10	10	10	10	10	10	10	10	10	10	10	10
CP	5	10	15	---	---	---	---	---	---	---	---	---
CCS	---	---	---	5	10	15	---	---	---	---	---	---
SSG	---	---	---	---	---	---	5	10	15	---	---	---
Indion 414	---	---	---	---	---	---	---	---	---	5	10	15
MCC	140	140	140	140	140	140	140	140	140	140	140	140
Mannitol	41	36	31	41	36	31	41	36	31	41	36	31
Aerosi l	2	2	2	2	2	2	2	2	2	2	2	2
Stearic acid	2	2	2	2	2	2	2	2	2	2	2	2
Total weight(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of Domperidone Fast dissolving Tablets:

Pre-compression parameter:

The uniformly mixed powders of all formulations were evaluated for following parameters before compression.

Angle of repose (θ) [7:]

The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is used to find the flow properties of powder and calculated using an equation 1

Equation 1 Tan θ = tan-1 (h/r)

Where, θ is the angle of repose, H is the height in cm, R is the radius in cm.

b) Bulk density (Db) [8]:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring Cylinder and the volume was noted. It is expressed in gm/ml and is determined by an equation 2

Equation 2 Db=M/V0

Where, M is the mass of powder, V0 is the bulk volume of the powder

c) Tapped Density (DT):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is determined by an equation 3

Equation 3 DT=M/V1

Where, M is the mass of powder, V1 is the tapped volume of the powder.

d) Carr's index/compressibility index: Carr's Index is measured by using the values of the bulk density and tapped density by an equation 4

Equation 4 Carr's index= Tappeddensity-Poured density/Tapped densityx100

e) Hausner's ratio: Based on the tapped density and bulk density the hausner's ratio of the tablet blend was computed by an equation 5

Equation 5 Hausner's ratio (H) =Tapped density / Bulk density

Post compression parameters [9. 10. 11]:

Then the tablets were evaluated for following parameters

a) Thickness:

Thickness was determined for 20 pre weighed tablets of each batch using a vernier calipers scale and the average thickness was determined in mm.

b) Hardness:

Hard ness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in Kg/cm². Five tablets of each formulation were randomly picked and hardness of the each tablet was determined. Then the average hardness value was calculated.

c) Weight variation test:

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications, when not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

d) Friability test:

The friability of tablets were determined using Roche friabilator. It is expressed in percentage (%). 10 tablets were randomly selected and their initial weight was noted. Then tablets were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were taken out the weight was noted again. For conventional tablets the percentage loss in friability should be less than 1% where as friability values of up to 4% are acceptable for oral disintegrating and chewable tablets.

e) Wetting time:

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. It can be measured using the following procedure.

Procedure: Five circular tissue papers of 10cm diameter were placed in a Petri dish with 10cm diameter. 10ml of water was added to Petri dish, a tablet was carefully placed on the surface of the tissue

paper. The time required for water to reach upper surface of the tablet was noted as wetting time [8].

f) Water absorption ratio(R):

The weight of the tablet in the above procedure before keeping in to the Petri dish was noted (Wb). The wetted tablet from the Petri dish was taken and re weighed (Wa) using the same. The Water absorption ratio(R) was determined according to the following. [9]

Equation 6 R=100(Wa-Wb)/Wb

g) Drug content uniformity:

The content uniformity test is used to ensure that every tablet contains the labeled amount of drug substance intended with little variation among tablets within a batch.

Five tablets were selected randomly and average weight was determined. Tablets were crushed in a mortar and accurately weighed, amount of average tablet was taken from the crushed blend. Then, the sample was transferred to the 100ml volumetric flask and was diluted up to the mark with 0.1NHCl. The content was shaken periodically and kept for 24 hours for dissolution of drug completely. The solution was filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λmax of 284.0nm against 0.1NHCl as a blank reference using UV-Visible spectrophotometer.

H) *In-vitro* disintegration time:

Disintegration time is the time taken by the tablet to break into smaller particles. The disintegration test is carried out using USP disintegration test apparatus containing a basket rack assembly with six glass tubes which consists of a 10 mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900ml of 0.1NHCl which is maintained at 37±2°C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet. And the time for disintegration of FDTs were tabulated.

i) *In-vitro* dissolution studies:

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines percentage of the drug in a tablet dissolved under specified conditions in a specified time.

In-vitro drug release studies were carried out using USP dissolution test apparatus II (paddle type) at 50 rpm. The drug release profile was studied in 900ml of 0.1N HCl maintained at 37±0.5°C. 5 ml of dissolution medium withdrawn at specific time intervals (5, 10,15,20,25 and 30 minutes) and filtered.Then the amount of drug released was determined by UV-Visible spectrophotometer. 5ml of fresh 0.1N HCl was replaced as soon as the drug samples were withdrawn. Then the percent drug dissolved was calculated for different time intervals. It was conducted in triplicate and average percent drug release was calculated**.**

Short-term stability testing of fast dissolving tablets:

The stability studies were carried out on the most satisfactory formulations as per ICH guideline Q1C. The most satisfactory formulation was filled in high-density polyethylene bottle which is sealed with aluminum packaging and kept in the humidity chamber maintained 40 ± 2°C/75% ± 5% relative humidity (RH) for 3 months.

3. RESULTS AND DISCUSSIONS

***ATR studies*:**

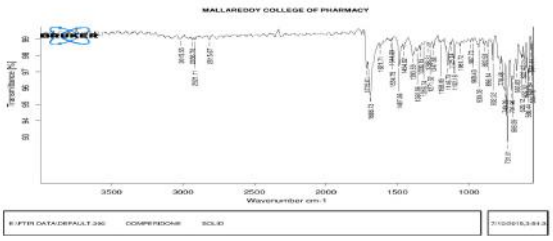

Fig 1: ATR spectrum of domperidone

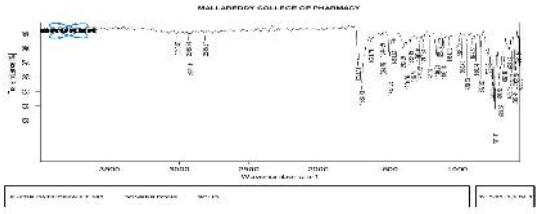

Fig 2: ATR spectrum of Domperidone and excipient

ATR Spectrum of pure drug (Domperidone) and mixture are presented in the fig no 1, and 2 respectively. Pure drug has shown sharp characteristic band at 1688,832 and 731 cm^{-1} due to carbonyl group, C-H bending and C-C stretching respectively. It was observed that there was no change in these main bands due to the presence of excipients. ATR studies revealed that there is no physical and chemical interaction between drug and excipients.

Pre-compression parameters:

Table 2: Results of pre compression parameters.

Formulation code	Angle of repose (θ)	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	Carr's index (%)	Hausner's ratio (%)
F1	29.5±0.8	0.74±0.4	0.88±0.5	15.9±0.9	1.189±0.7
F2	29.1±1.2	0.74±0.3	0.86±0.5	14.4±1.0	1.162±1.1
F3	27.2±0.1	0.71±1.0	0.83±0.9	13.9±0.9	1.169±0.8
F4	30.1±0.7	0.68±0.7	0.79±0.5	13.9±1.1	1.161±0.9
F5	28.7±1.0	0.74±0.3	0.86±0.4	13.9±0.6	1.162±0.8
F6	29.8±0.2	0.72±0.2	0.84±0.3	14.2±0.3	1.166±0.5
F7	30.2±0.6	0.78±0.8	0.88±0.8	11.3±0.8	1.12±1.0
F8	26.5±0.3	0.75±0.9	0.89±0.8	15.7±0.9	1.186±1.1
F9	27.7±0.2	0.79±1.0	0.91±1.1	13.1±0.7	1.151±0.9
F10	25.5±0.3	0.75±0.5	0.83±0.6	9.14±0.9	1.106±0.8
F11	28.6±0.9	0.72±0.9	0.78±0.8	14.5±0.4	1.08±0.5
F12	28.8±0.2	0.70±0.5	0.81±0.6	13.5±0.6	1.157±0.8

(n=3 MEAN±SD)

The values for angle of repose were found to be within the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be within the range of 0.68 to 0.79 (gm/cm^2) and 0.79 to 0.91 (gm/cm^2) respectively. Carr's index was found to be within the range of 9.14% to 15.9%. The Hausner [s] ratio was within the range of 1.08 to 1.18 as shown in table 2 from the result. It was concluded that the powder blends have good flow properties .which confirms the uniform filling during compression into tablets.

Post compression parameters:

Table3: Results of post compression parameters.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation	% Friability	Wetting time (sec)	Water absorption ratio
F1	3.5±0.1	2.1±0.1	199.8±0.9	0.74±1.1	23±1.0	110±0.9
F2	3.5±0.1	2.1±0.1	200.1±0.8	0.94±0.6	22±1.0	130±1.1
F3	3.5±0.1	2.1±0.1	202.4±1.2	0.84±0.8	19±1.0	135±1.3
F4	3.5±0.1	2.1±0.1	200.4±0.7	0.75±1.2	24±1.0	100±0.7
F5	3.5±0.1	2.1±0.1	202.1±1.2	0.99±1.0	23±1.0	130±1.3
F6	3.5±0.1	2.0±0.2	199.8±1.2	0.11±1.1	20±1.0	141±0.8
F7	3.5±0.1	2.1±0.1	199.9±0.9	0.83±0.6	25±1.0	90±1.2
F8	3.5±0.1	2.1±0.2	200.3±1.1	0.66±0.9	23±1.0	91±0.6
F9	3.5±0.1	2.0±0.2	200.3±1.1	0.84±1.0	20±1.0	95±0.8
F10	3.5±0.1	2.0±0.3	201.1±1.3	0.82±0.9	20±1.0	112±1.2
F11	3.5±0.1	1.9±0.2	202.1±0.4	0.83±1.0	18±1.0	125±1.4
F12	3.5±0.1	1.8±0.3	199.5±0.7	0.66±0.6	16±1.0	155±0.7

(n=3 MEAN±SD)

Hard ness for all the formulations were in range of 1.8 to 2.1 kg/cm^2, it indicated that all the formulations possess sufficient mechanical strength .Weight variation was found to be within IP limits. Friability values were found to be less than 1% indicated that within the IP limits. Wetting time of all the formulations was found to be in the range of 16 to 23 seconds, and Water absorption ratio of all the formulations was found to be within the range of 90 to 155. Among all the formulations, F12 formulation has shown least wetting time and highest water absorption ratio may be due to high concentration of Indion 414 (cationic exchange resin) .which swells easily by absorption of water.

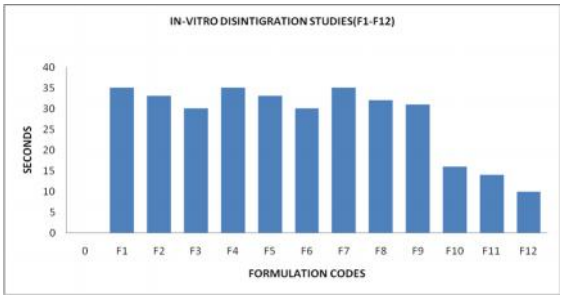

Fig 3: In vitro Dissolution study of all formulations

In vitro disintegration time of all formulations was in the range of 10 to 35 seconds as shown in fig 3. Among all the formulations (F10-F12) containting cationic exchange resin (Indion as superdisintegrant) showed rapid disintegration with low disintegration time of 10 to 16 seconds due presence of indion as superdisintegrant. Because indion was having remarkable swelling and moisture absorbing capacities. Hence disintegration time was less than other formulations [12] .F12 has shown least disintegration time may be due to high concentration of Indion as per in fig 3.

In vitro drug release studies shown in table 4, 5. It revealed that drug release rate was increased with increasing concentration of superdisintegrants. Among all the formulations F12 formulation in which Indion used as super disintegrant(cationic exchange resin) increased drug release rate compare to other superdisintegrants, may be due to the presence of cationic exchange resin which has remarkable swelling and moisture absorbing capacities. Hence disintegration was rapid, thus it F12 formulation has faster drug release than other formulations. Hence F12 formulation was selected as best or optimized formulation. As 100% was released within 20 minutes.

Table 4: *In-vitro* dissolution profile of formulation F1 to F6

Time(min)	F1	F2	F 3	F4	F5	F6
0	0	0	0	0	0	0
5	52.24±0.9	56.78±1.0	58.68±0.2	52.28±1.0	55.21±1.2	57.4±0.2
10	71.08±0.3	73.8±0.5	75.5±1.2	66.24±1.1	69.2±1.0	73.34±0.6
15	80.75±0.2	82.57±0.2	83.56±0.6	78.74±0.9	79.5±1.3	81.4±0.5
20	88.4±0.5	90.34±0.4	93.96±0.4	85.35±1.2	90.0±1.1	92.9±1.0
25	95.48±1.0	97.5±1.2	99.5±1.1	93.6±1.1	96.46±0.6	98.35±0.2

(n=3 MEAN±SD)

Table 5: *in-vitro* dissolution profile of formulation F7 to F12

Time(min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	50.47±0.4	52.69±0.7	55.67±0.7	66.7±1.0	68.7±1.1	70.91 ±0.9
10	66.47±0.2	71.70±0.5	74.95±0.4	74.9±1.0	75.3±1.2	78.84 ±0.4
15	77.58±0.6	81.58±0.6	81.86±0.7	92.5±1.1	95.5±1.1	98.17±1.0
20	84.8±0.7	89.59±0.3	93.24±0.6	98.36±0.5	99.71±0.6	101.34±0.5
25	92.69±0.2	95.48±0.8	97.86±0.3			

(n=3 MEAN±SD)

Table 6: Results of stability studies of optimized formulation (F12)

Parameter	1 month	3 months
Thickness (mm)	3.5±0.1	3.5±0.1
Hardness(kg/cm²)	1.8±0.3	1.8±0.2
Weight variation	199.5±0.6	199.3±0.5
% friability	0.65±0.5	0.64±0.6
Wetting time(sec)	16 ±0.3	16±0.4
Water absorption ratio	155±0.6	153±0.1
Assay(%)	101.1±0.5	10±0.4
*In-vitro*disintegration time(sec)	10±0.3	10±0.5

Table 7: In-*vitro* dissolution study of optimized formulation (F12) during stability study

Time (Min)	Percent drug release(%)(1month)	Percent drug release(%)(3month)
0	0	0
5	70.90±0.8	70.88±0.9
10	78.84±0.2	78.79±0.4
15	98.17±0.9	98.15±1.0
20	101.32±0.2	101.30±0.5

Stability studies of optimized formulation:

The results of Short term stability studies indicated that the post compression parameters are satisfactory within the limits after storage for 3 months. *In vitro* drug release profile also not changed on storage. Hence stability studies confirmed that the prepared formulation (F12) is stable.

4. CONCLUSION

From the above results and discussion, it can be concluded that the FDT of Domperidone using Indion 414 as superdisintegrant is stable and best formulation

as it has disintegrated within 10 seconds and 100% drug release was achieved within 20 minutes. Hence the preparation of FDT of Domperidone with Indion 414 was successful.

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