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RESEARCH ARTICLE

Formulation and in vitro evaluation of sustained release domeperidone – Indion 244 complexes

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SUMMARY

Domperidone is a prokinetic agent used for treatment of nausea and gastro-esophageal reflux disease (GERD). The purpose of this study is to formulate sustained release DRCs of domperidone which will provide the patient compatibility and sustained plasma levels.
The study involves preparation of sustained release drug-resin complex (DRCs) of domperidone & study effects of various parameters like pH , ionic strength of dissolution medium, particle size of DRC, drug content of DRC on release of domperidone from DRC & also drug release from DRC with unloaded weak resin. Drug loading was carried out by batch method. DRCs were evaluated for physical properties & invitro drug release. DRCs provided sustained release domperidone. IR and X-ray studies indicate complexation of drug and resin along with monomolecular distribution of drugs in amorphous form in resin matrix. DRC showed good flow properties. In-vitro drug release gave desired release profiles from test DRC. The novelty of work is that if combination is used then retardation in release of domperidone from DRCs is achieved by presence of weak resin in the formulation. For sustaining the release there is no need of further microencapsulation or coating of drug resin complex.

Key Words: *Domperidone, drug-resin complex (DRCs), Indion 244, sustained release.*

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Domeperidon'un formülasyonu ve in vitro sürekli salım değerlendirmesi – İndion 244 kompleksleri

ÖZET

Domperidon, mide bulantısı ve gastro-özofegal reflu (GERD) tedavisinde kullanılan prokinetik bir ajandır. Bu çalışmanın amacı, domperidon ile sürekli salım yapan ilaç-reçine komplekslerinin formüle edilerek hasta uyuncunun ve sürekli plazma seviyelerinin sağlanmasıdır. Çalışmada domperidon ile ilaç-reçine kompleksleri hazırlanmış, pH, disolüsyon ortamının iyonik şiddeti, hazırlanan komplekslerin partikül büyüklüğü ve kompleksin içerdiği ilaç miktarı gibi çeşitli parametrelerin, ilaç-reçine komplekslerinden ve ayrıca kompleks oluşturulmayan zayıf reçineden domperidon salımı üzerine etkileri incelenmiştir.
İlaç yükleme yığın metoduyla gerçekleştirilmiştir. Hazırlanan ilaç-reçine komplekslerinin fiziksel özellikleri incelenmiş ve komplekslerden in vitro ilaç salım çalışmaları gerçekleştirilmiştir. İlaç-reçine kompleksleri ile domperidonun sürekli salımı sağlanmıştır. IR and X-ray çalışmaları, reçine matriksinde , amorf formda bulunan ilaçların, ilaç-reçine kompleks oluşumunun monomoleküler dağılım ile gerçekleştiğini, işaret etmiştir. İlaç-reçine kompleksleri iyi akış özelliği göstermiştir. İn vitro salım çalışmaları ile hedeflenen salım profilleri elde edilmiştir. Formülasyonda zayıf reçine de ilaç-reçine kompleksleriyle Sürekli salım sağlamak için ise ilaç-reçine kompleksinin herhangi bir mikroenkapsülasyon veya kaplama işlemine gerek yoktur.

Anahtar kelimeler: *Domperidon, ilaç-reçine kompleksi (DRCs), Indion 244, sürekli salım.*

INTRODUCTION

Several techniques are reported for sustained release drug delivery using ion exchange resins, where the drug resin complex (DRC) dissociates slowly in GI fluids to give sustained release(1,2). Domperidone (DMP), a dopamine antagonist, used in the treatment of nausea and vomiting with dose range of 10–40 mg daily in three divided doses. The elimination half life is 5–7 h(3). Domperidone is a weak base which when formulated as oral sustained release dosage form may get precipitated as poorly soluble free base within the formulation when exposed to environments of increasing pH, in the intestinal fluid adversely affecting the drug release (4,5). A possible approach for ensuring pH independent sustained release of DMP is preparation of DRC.

Controlling the rate of drug release by modifying release properties of DRC can be effected by coating the resin beads (6-9), the pattern of drug release is governed

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by the properties of the coat. Usually DRC are coated with insoluble polymers which control the release of drug by diffusion mechanism, however, DRC combined with unloaded resin particles may also represent a useful tool for improving their release and protective properties(10).

In the present study, a system based on the DMP resin complex with Indion 244(matrix type styrene/DVB styrene and divinyl benzene co- polymer, functional group SO_3^-, standard ionic form H^+) has been and evaluated for achieving pH independent sustained release of DMP. The aim of this study was to evaluate the *in-vitro* release behaviour from DRC in presence of unloaded weak resin and also to study the effect of some variables such as the pH & ionic strength of dissolution medium, particle size & drug content of DRC on the release of domperidone from DRC.

MATERIALS AND METHODS:

Materials

Domperidone (DMP) was a kind gift from BURGEON Pharmaceuticals Pvt. Ltd, Mumbai, Indion 244 was provided by Ion exchange India Ltd. All other chemicals were of AR grade and purchased from local market.

Methods

Preparation and evaluation of DRCs

DMP (100mg) was slurried in 100 ml deionized water along with required quantity of Indion 244 and stirred till attainment of drug equilibrium which was determined spectrophotometrically by measuring concentration of drug remaining in solution. Resinate thus formed was washed with an excess amount of deionized water, which was collected and added to previous filtrates. Resinates were dried overnight in a hot air oven at 50^{O}C and then stored in tightly closed in desiccator. The drug content in the combined solution of final filtrate and washing was analyzed by UV-Visible double beam spectrophotometer (V530, Jasco) at a λ max 284 nm. The amount of drug adsorbed was determined by the difference between amount of drug present in stock solution and amount remaining in filtrate at the end of equilibrium (11).

Determination effect of pH on drug loading on Indion 244.

DMP Indion 244 (1:1), was slurried in deionized water and drug loading was determined at different pH such as 2,3,4,5,6 Resinates were collected by filtration, washed with100 ml deionized water to remove uncomplexed drug and dried at 50^{O}C. Drug content in filtrate & washing was determined as mentioned previously in Preparation and evaluation of DRCs.

Effect of drug: resin ratio on drug loading on Indion 244

DMP and Indion 244 in ratio such as 1:1, 1:1.5, 1:2 was slurried in deionized water at predetermined pH and drug loading was determined as mentioned in Preparation and evaluation of DRCs.

Evaluation of physical properties of resin and DRC's

Different physical parameters of DRC like shape, flow properties, bulk density, tapped density, packing ability were determined. The FT-IR studies were carried out using Jasco FT/IR-460. The X- ray diffraction studies were carried on Phillips analytical X-ray BV(PW 1710) using cu anode 40 kv voltage and 30 ma current (12).

Determination of selectivity coefficient of Indion 244

The ion exchange process is an equilibrium reaction. The position of equilibrium was measured by the selectivity coefficient formulae, defined as follows,

$$K_{DM} = \frac{[D]r \times [M]s}{[D]s \times [M]r}$$

Where,

[D]s, [M]s and [D]r, [M]r represents the concentration (meq/ml) of drug and cations, in the solution and resin phase at equilibrium respectively. *[M]r* is equal to concentration of ionized sites on resins less those occupied by the entrapped drug. Then *[M]s* can be obtained by substracting *[M]r* from total cations (13).

In-vitro drug release from DRC

DRC of DMP with Indion 244 were subjected to *in-vitro* dissolution studies using USP type II (paddle) apparatus at 100 rpm. Dissolution medium was 900 ml 0.1 N HCl at 37 ± 0.5 °.

Effect of DRC particle size on in-vitro DMP release from DRC

Particle size separation of DRC was carried out using sieving method. Different sieve fractions (oversize) were collected and *in-vitro* drug release from each sieve fraction was determined as described previously.

Effect of pH on in-vitro DMP release from DRC

A claimed advantage of ion exchange delivery system is that release of drug is independent of pH of the dissolution medium. This prospect was investigated by carrying out *in-vitro* drug dissolution studies in O.1 N HCl & pH 6.8 phosphate buffers.

Effect of ionic strength on In-vitro release from DRC

To study the effect of ionic strength on *in-vitro* release of drug from DRC, 0.1 N HCl buffer with ionic strength adjusted to μ = 0.1 and 0.4 were prepared using NaCl and drug release was determined.

Effect of percent drug content on In-vitro from DRC

To obtain DRC with different drug content, DMP and Indion 244 was stirred for 1, 2, 3 & 4 h respectively and filtered followed by determination of drug content and in-*vitro* release as described previously.

In-vitro DMP release from combination of loaded DRC with unloaded weak resin (Indion 294) in 1:1 ratio

DMP DRC was subjected to *in-vitro* dissolution study under conditions described previously in presence of weak resin (Indion 294) in 1:1 ratio

RESULT AND DISCUSSION

Preparation and evaluation of DRCs

A batch process was used for drug loading. Optimum period for attainment of equilibrium loading of domperidone was found to be 4 hours from preliminary experiments. The drug loading was carried out at 1:1 drug resin ratio using Indion 244 which gave 48.44% of content of domperidone (DMP).

Effect of pH on drug loading on Indion 244

The pKa of DMP is 7.9, as per pH partition hypothesis it is ionized at pH values between 1-6. The resin Indion 244 which possess sulfonic (strong acid) moiety will also be ionized irrespective of pH changes. This supports the observation that pH didn't have a pronounced effect on drug loading (Table 1) hence the default pH of drug dispersion in water i.e. 5 was maintained.

Table 1. Effect of pH on DMP loading on INDION 244 (mean ± S.D., n = 3)

pH	Domperidone loading on Indion 244
2	91.0 ± 0.30
3	90.0 ± 0.33
4	93.0 ± 0.45
5	93.46 ± 0.14
6	91.40 ± 0.34

Effect of drug: resin ratio on drug loading on Indion 244

It was observed that as the quantity of resin in complexation is increased the % drug content per gram resinate decreases (Figure 1). Since 1: 1 ratio gives drug content (48.44%) which was greater than the ratios containing higher amount of resin (38.50%) it was chosen for further studies.

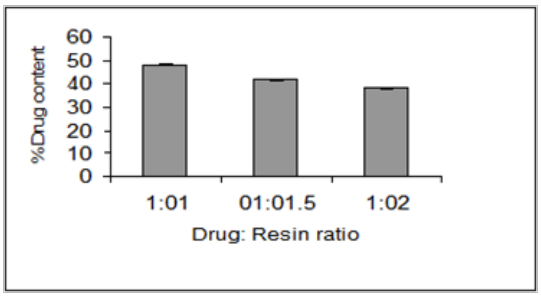

Figure 1. Effect of drug: resin ratio on % domperidone content on Indion 244. % Drug content

Evaluation of physical properties of resin and DRC's

The shape of DRC affects the flow and packing properties & was found to be irregular for Indion 244 and DRC. (Table 2) Angle of repose was in between 20-30° thus exhibiting good flow properties. Bulk density less than 1.2 gm/cm^2 exhibit good packing ability. Thus the results showed that resin and DRC exhibit good flow properties. Carr's compressibility index i.e. % compressibility and Hausner ratio indicates the packing ability of powders. When compressibility index ranges from 5 to 16 and Hausner ratio closer to 1 the material has good flow property and packing ability.

Table 2. Physical properties of indion 244 & DRC

Parameter	Indion 244 Resin	Resinate
Shape	Irregular	Irregular
Angle of repose	26.56	24.22
Bulk density	0.681	0.550
Tap density	0.789	0.610
Carr's index	15.85	13.27
Hausner ratio	1.15	0.98

The X–ray diffraction pattern for domperidone contained number of sharp peaks (A), while the resin showed a diffused peak or halo pattern (B), where as the resinate showed hump like diffraction pattern (C) (Figure 2) which indicates amorphous structure.

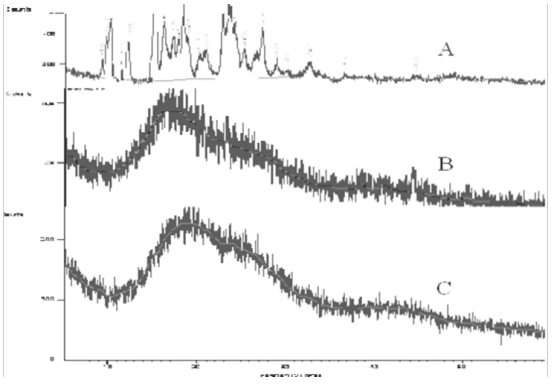

Figure 2. X-ray powder diffraction pattern , X-ray powder diffraction pattern of **A.** domperidone, **B.** Indion 244, **C.** domperidone resinate

According to this data molecular state of domperidone is crystalline, but that of resin is amorphous. The molecular state of domperidone prepared as drug resin complexes was changed from crystalline state to amorphous state, the drug molecule, which was outside the resin bead, did not disperse monomolecularly and so the crystalline state of domperidone was presented (14). This shows that entrapped drug molecule is monomolecularly dispersed in resin bead.

Similarly in the IR spectra domperidone shows peak at 3349 cm^{-1} corresponding to the N-H stretching in a secondary amine. IR also shows peaks corresponding to –COOH dimerization of drug in the range of 2500-3000 cm^{-1} (Figure 3).

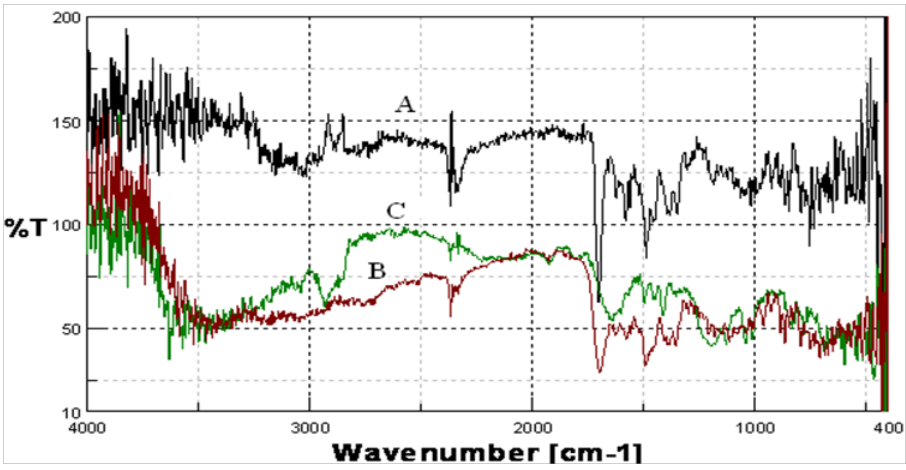

Figure 3. Infrared spectras of A. Domperidone, B. Indion 244, C. domperidone resinate

The absence of peak at 3349 cm^{-1} in resinate confirms the complexation of the secondary amine group in the drug with resin. The peaks representing amino group of the drug (3349 cm^{-1}) and the peak at 2900 cm^{-1} corresponding to –OH stretching in drug and the peak representing sulfonic group in resin are absent in resinate, which signifies that there was interaction of the amino group of drug with the sulfonic group of resin during resinate formation.

Determination of selectivity coefficient of Indion 244

Determining the selectivity coefficient was helpful to ascertain whether the ion exchange process attains equilibrium. K^D_M increased rapidly up to four h (Figure 4) although H^+ release in case of Indion 244 was not much seen after four h, high values of K^D_M between 3-4 h point to involvement of phenomenon other than ion exchange, such as Van der Waals forces or chemisorption. Hence, four h contact time between drug and resin was determined to be optimum to equilibrate the ion exchange process to achieve maximum drug loading (15).

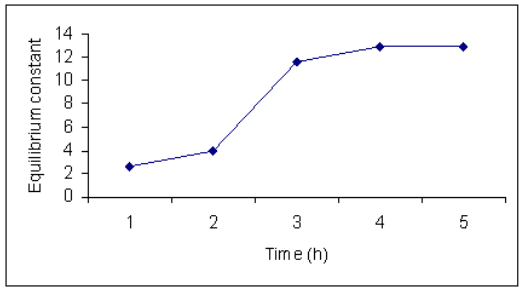

Figure 4. Selectivity coefficient for Indion 244 with time

Figure Legend ; Indion 244

In-vitro drug release from DRC

The *in-vitro* dissolution profile (Figure 5) shows that drug release from DRC (1:1) was 43.41%, 84.17% at the end of 1st and 8th h respectively. Whereas DRC 1:1.5 & 1:2 released about 40.21 % & 35.31% of drug in 1st hour and 100.63 % & 87.95% of drug was released at the end of 8th h. The DRC (1:1) showed initial high release but could retard the drug release beyond 8 h therefore DRC of 1:1 ratio showed potential to sustain the release of drug. The initial burst release may be owing to the DRC of lower particle size (15).Therefore further studies were undertaken to investigate the effect of particle size on drug release.

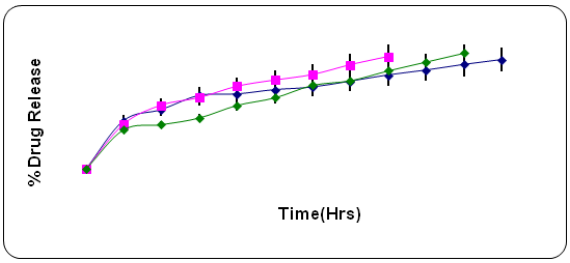

Figure 5. In-vitro release profile of domperidone from domperidone resonates

Resinate 1: 1 Resinate 1:1.5 Resinate 1:2

Effect of DRC particle size on in-vitro DMP release from DRC

The table (Table 3) below shows that resinate of mean particle size diameter 75 µm releases 86.64% of domperidone in 8 h, while resinate of mean particle size diameter 105 µm & 125 µm released 75.86% & 75.93% of domperidone in 8 h. This shows decrease in domperidone release as the diameter of resin bead increased. This is due to increase in diffusive path length of drug with increase in resin bead diameter; similar observations are reported in literature (16).

Table 3. Effect of particle size of resinate on in-vitro Domperidone release (Mean ± SD, n=3)

Time (Hrs)	75 µm	105 µm	125 µm
1	30.31±0.41	28.19±0.91	25.27±1.25
2	39.07±1.12	37.08±1.03	35.42±0.31
3	46.22±0.32	44.98±0.39	43.25±0.94
4	51.78±0.75	48.15±0.79	46.83±0.64
5	57.35±0.24	55.81±0.36	54.30±0.79
6	75.24±0.14	63.21±0.29	62.09±0.55
7	78.50±0.63	69.86±0.96	68.95±0.36.
8	86.64±0.37	75.86±0.88	75.93±1.36
9	94.87±0.94	82.80±0.86	81.92±1.9
10	102.39±0.82	87.46±0.59	88.90±1.37
11	--	96.47±0.68	96.88±0.17

Effect of pH on in-vitro DMP release from DRC

Figure 6 shows the drug release in 0.1 N HCl & phosphate buffer (PB) was determined keeping ionic strength (µ) constant at 0.1, no effect of pH on release of domperidone from resinate was evident (9-11). The dissolution data was subjected to paired t test using Instat 3.0 software. The mean of the differences between column A and column B was found to not significantly different from zero. The one-tailed P value is 0.2457, considered not significant (t = 0.7143 with 10 degrees of freedom) at 95% confidence interval. Thus no significant difference between domperidone release in 0.1 N HCl & PB pH 6.8 was observed.

Hence the pH independent release of domperidone from domperidopne resinate can be obtained.

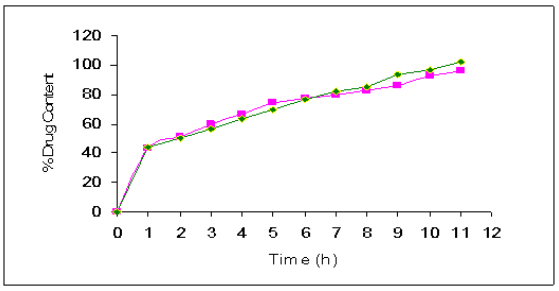

Figure 6. Effect of pH on in-vitro domperidone release from domperidone resinate

0.1 N HCl; PB pH 6.8

Effect of ionic strength on In-vitro release from DRC

Since ion exchange is an equilibrium phenomenon the ionic strength should have effect on position of equilibrium & thus rate & extent of drug release was 86.22 % drug released in 8 h with ionic strength of 0.1 (A), while 91.17 % drug released in 8 h with ionic strength of 0.4(B) (Figure 7) The dissolution data was subjected to paired t test using Instat 3.0 software. The mean of the differences between column A and column B was found different significantly from zero. The one-tailed P value is 0.0083, considered significant (t = 2.935 with 9 degrees of freedom) at 95% confidence interval.Thus it was observed that increasing ionic strength enhances liberation of domperidone from resinate. This is due to the increase in influx of competitive ions which influence rate of drug release (17).

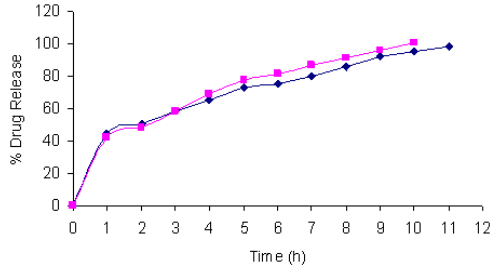

Figure 7. Effect of ionic strength (µ) on in-vitro domperidone release in 0.1 N HCl from domperidone resinate A: µ= 0.1; B: µ= 0.4

Effect of percent drug content on In-vitro from DRC

The result shows in Figure 8 that about 69.24 %, 74.43 %, 76.20 % and 83.06 % drug was released in 8 h from resinates of 38 %(A), 42.43 %(B), 45.19 %(C) and 48.44 %(D) drug content respectively.

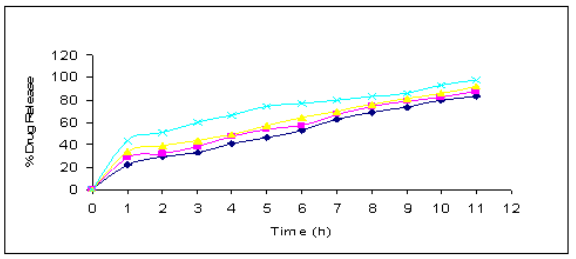

Figure 8. Effect of percent drug content on in-vitro domperidone release from domperidone resinate

A: 38%; B:42.43%; C: 45.19%; D: 48.44%

The data was subjected to statistical treatment (ANOVA) followed by Tuckey test , the P value is < 0.0001, considered extremly significant.Thus it was observed that increased percent drug content of resinate increases the release of drug from resinates. This might be due to the increase in influx of competitive ions which influence rate of drug release.

On the basis of performed studies domperidone resinate with 1:1 drug resin ratio, 125µm particle size and 48.44% drug content was chosen to prepare final formulation.

In-vitro DMP release from combination of loaded DRC with unloaded weak resin (Indion 294) in 1:1 ratio

It is reported in literature (15) that release of drug from resinate can be controlled in presence of unloaded resin. Hence domperidone resinate (1:1) ratio of mean diameter 125 µm was subjected to dissolution with unloaded 294 a weak cation exchange resin. The retardation of drug release with increase in quantity of unloaded weak resin was seen (Table 4). This might be due to adsorption of drug released from resinate on the unloaded weak resin. The drug adsorbed on weak resin was further released & drug release at the end was not affected considerably.

Table 4. *In-vitro* Domperidone release profile from resinate with weak resin (in different ratios)(mean ± sd, n=3)

Time (h)	% Release from ratio 1:0.5	% Release from ratio 1:1
1	34.16±1.2	14.42±0.76
2	44.75±1.04	29.14±0.39
3	53.78±1.01	41.95±0.92
4	61.75±0.98	48.49±0.83
5	67.42±0.45	53.20±0.84
6	72.21±0.74	59.27±0.85
7	80.76±0.47	63.40±0.68
8	89.20±0.86	70.29±0.28
9	93.70±0.49	80.07±1.02
10	101.50±0.98	86.89±1.05

CONCLUSION

From above work it can be concluded that, Domperidone (DMP) release from DRCs follows pH independent profile. DMP release from DRC is dependent on particle size of DRC. Increasing ionic strength enhances liberation of DMP from DRC, higher drug content of DRC affords faster release of drug from DRCs. Drug release can also be controlled by including unloaded weak resin; there is retardation of drug release with increase in quantity of unloaded weak resin thus the drug release can be controlled by including a weak resin instead of further microencapsulation or coating of drug resin complex as reported in literature.

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