

FORMULATION AND STABILITY OF ISOSORBIDE DINITRATE GEL

This study aimed to formulate a gel suitable for rectal use, whose pharmacological action would induce smooth muscle relaxation of the internal anal sphincter and thus promote symptomatic relief and healing of anal fissures, anal fistulae and haemorrhoids. A formulation consisting of isosorbide dinitrate injection (100 mL), sodium benzoate (100 mg) and Bard[®] absorption dressing (3 g) gave a gel of suitable consistency, which was the most successful judged by the percentage extraction (72.4±4.9) of the isosorbide dinitrate achieved. Furthermore, no degradation products were seen up to 69 days after formulation. There was no difference at the 95% confidence level between the percentage of isosorbide dinitrate extracted from the gel formulation stored in glass vials compared with that stored in the Sherwood polypropylene syringes, suggesting that no sorption had taken place to the container. The efficiency of the gel in relaxing the anal sphincters has been shown by measurements of the internal and external sphincter pressures: clinical use of the gel, although unreported here, has proved very successful.

KEY WORDS: Formulation, stability, rectal gel, isosorbide dinitrate, anal fissures, haemorrhoids

INTRODUCTION

Organic nitrates have been used for the treatment of angina pectoris since 1867 [1]. These preparations can be administered orally [2], sublingually [3], intravenously [4] and transdermally in the treatment and prophylaxis of this condition, vasospastic angina [4] and congestive heart failure [5].

Organic nitrates have multiple potential mechanisms of action [6]. At a cellular level it is thought that these compounds are converted intracellularly to nitric oxide and 5-nitrosothiol via an interaction with sulphhydryl groups. Nitric oxide and perhaps 5-nitrosothiol activate soluble guanylate cyclase to increase intracellular concentration of cyclic GMP. Increased cyclic GMP induces a sequence of protein phosphorylation associated with reduced intracellular calcium release from the sarcoplasmic reticulum or reduces permeability to extracellular calcium, thus smoothing muscle relaxation [7]. This action of organic nitrates on the internal anal sphincter, resulting in a reversible "chemical sphincterotomy", documented in earlier clinical and monometric trials [8,9], could prove beneficial to aid examination, symptom relief and eventual cure in painful conditions such as anal fissure, anal fistulae and haemorrhoids, where anal spasm plays a common role. Indeed Lund and Scholefield [10] forecast that glyceryl trinitrate (GTN) ointment might soon replace surgery as first line treatment for chronic anal fissure.

Piles are associated with an enlargement and inflammation of the haemorrhoidal cushions which may prolapse and also bleed during defaecation, and this condition may also well respond to this therapy.

Anal fissure is essentially a linear tear in the distal anal canal. When such tears become chronic they respond poorly to medical regimens and surgical sphincterotomy is generally preferred to provide symptomatic relief and healing. These surgical procedures and the theories for their success have been outlined by Simons and Beart [11]. However, successive lateral internal sphincterotomies can lead to faecal incontinence, while the procedure is also extremely painful, so it would be desirable to have a

topical preparation which could be applied to the anal canal to achieve a similar effect.

The aims of this study were to formulate a gel suitable for rectal use, whose pharmacological action would induce smooth muscle relaxation of the internal anal sphincter. Isosorbide dinitrate was chosen because an injection preparation which could be incorporated into a gel formulation was readily available. The suitability of the formulation was investigated by determining the possible percentage extraction of the active agent from the gel into distilled water, as it was thought that ease of extraction might be directly proportional to the product's ability to exert a pharmacological effect. However, it is acknowledged that this premise may be incorrect considering that the rectum contains only 2–3 mL of mucous secretions.

Therapeutic potential of the gel was investigated in clinical use.

MATERIALS AND METHODS

The isosorbide dinitrate injection was purchased from the pharmacy department, University Hospital of Wales (formula: isosorbide dinitrate 25% in lactose 0.4g, ethanol 90%, 0.55 mL, sodium chloride 0.9 g, freshly distilled water to 100 mL).

Preparation of isosorbide dinitrate gel for rectal use

Sodium benzoate (Merck) 100 mg, an antimicrobial preservative, was dispersed in the isosorbide dinitrate injection 100 mL and mixed until it had dissolved. Bard^â absorption dressing (Bard) @ 3 g, (a graft copolymer starch provided in dry flake form) was added and mixed to give the desired viscosity, (pH=7.0). The gel was packed into 2 mL disposable polypropylene syringes (Sherwood Medical) and the ends sealed with blind hubs.

A range of suspending agents had been investigated prior to arriving at this final formulation. These included, Methocel A4C Premium EP (Colorcon Ltd), produced from the cellulose fibres of cotton lint or wood pulp and sodium carboxymethylcellulose (Courtaulds Chemicals). The isosorbide dinitrate injection (2 mL) was added to the appropriate concentration of suspending agent (see Table 1) with a final volume of 20 mL

Suspending agent Percentage w/v	Percentage Extraction of isosorbide dinitrate
Methocel A4C 4.5 2.25 1.125 (n=1,cc=0.999)	5.3 11.1 22.1
Sodium Carboxymethylcellulose 2.5 (n=1,cc=0.999)	3.7
Bard ^â absorption dressing 3.0 (n=3, two aliquots taken from each extraction)	72.4 ± 4.9 D

Table 1. Summary of percentage extraction of isosorbide dinitrate from various concentrations of suspending agents. D for Bard absorption dressing formulation, the mean extraction with the sample standard deviation is shown, cc=0.996.

Extraction of the isosorbide dinitrate from the gel

Isosorbide dinitrate was extracted by filtering twice, using a Buckner funnel, a known concentration of a vigorously shaken solution of the gel (~2 g) in distilled water (to 20 mL). First a glass microfibre filter (Whatman) was used, then a 0.2 µm FP-Vertical[®] membrane filter (Gelman Sciences). Two aliquots of the pooled filtrate were then analysed.

High performance liquid chromatography analysis (HPLC) of isosorbide dinitrate

HPLC analysis was performed using a glass Chromsher C18 column (Chrompack) (10 cm x 0.9 cm external diameter) and a mobile phase of 40% w/v Hipersolv Methanol (BDH) and 60% w/v distilled water, at pH 5.90. The flow rate was 0.4 mL min⁻¹ and detection was by UV absorbance at 214 nm. The sample (25 µL) was injected in duplicate in order to determine the percentage extraction from the prepared gels. External calibration curves were constructed using freshly prepared isosorbide dinitrate in the range 0.5 to 1.2 mg mL⁻¹ (50–120% of stated contents), prior to injection of the samples. Correlation coefficients are shown in Tables 1 and 2.

Time after formulation (days)	Percentage extraction of isosorbide dinitrate
0	74.6
48	86.8
69	84.2

Table 2. Percentage extraction of isosorbide dinitrate from the Bard[®] absorption dressing formulation with increasing periods of time from formulation n=1. Two aliquots were taken from one extraction and analysed by duplicate injection cc = 0.996.

Stability assessment of gel formulation

The gel formulation, packed in Sherwood Medical syringes, was stored in the refrigerator at 6°C and the percentage extraction of the active agent was assessed over a 10-week period

Determination of whether the isosorbide dinitrate in the gel formulation was binding to the polypropylene syringes

A known weight of injection and Bard[®] absorption dressing was prepared and stored in Sherwood Medical syringes or glass vials, each with appropriate seals (n=3). After 2 days the isosorbide dinitrate was extracted and analysed.

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RESULTS

Table 1 shows the concentration of active agent extracted from each of the formulations. The formulation prepared using Bard[®] absorption dressing was found to be the most successful, judging by the percentage extraction (72.4±4.9) of the isosorbide dinitrate which was possible.

Table 2 shows the percentage extraction of the isosorbide dinitrate up to 69 days from formulation. Furthermore, no degradation products were seen at this time.

Table 3 shows the percentage of isosorbide dinitrate extracted from formulations stored in glass vials and in polypropylene syringes.

Percentage of isosorbide dinitrate extracted from formulation stored in glass vials	Percentage of isosorbide dinitrate extracted from formulation stored in polypropylene syringes
78.6	72.9
78.5	75.9
76.7	75.5

Table 3. Percentage extraction of isosorbide dinitrate from Bard^â absorption dressing formulation when stored in different containers for 2 days. Two aliquots were taken from one extraction and analysed by duplicate injection and mean result shown above, $cc=0.999$. Statistical analysis showed no difference at the 95% confidence level for the two sets of data.

CONCLUSIONS

- Bard^â absorption dressing was found to be the most suitable suspending agent. Absorption through the rectal mucosa is in accordance with the pH-partition hypothesis. Rectal fluids have a low buffer capacity and the pH in the lumen is governed by the pH of the formulation inserted. The active agent will be bound in the hydrogel, available for local use, while its systemic availability will be minimal.
- The isosorbide dinitrate gel formulation showed no breakdown 69 days after formulation (see Table 2). However, it is acknowledged that further studies are necessary to investigate and statistically quantify the variables in the method of extraction of isosorbide dinitrate from the Bard^â. Additionally, long term stability studies need to be carried out to detect any degradation products of the isosorbide dinitrate.
- Lee and Fenton-May [12] showed that isosorbide dinitrate was sorbed onto polyvinyl chloride bags and administration sets (resulting in substantial losses in potency) but was not sorbed by glass or polypropylene. This was confirmed in this study as no difference at the 95% confidence level was shown between the percentage of isosorbide dinitrate extracted from the gel formulation stored in glass vials compared with that stored in the Sherwood polypropylene syringes.

Clinical use of the gel, although not reported here, has produced excellent results. This is thought to be due to the relaxation effect of the isosorbide dinitrate gel on the anal sphincters.

ACKNOWLEDGEMENTS

The authors wish to acknowledge that the isosorbide dinitrate injection was purchased from the sterile products unit of the pharmacy department, University Hospital of Wales.

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