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Equipment for drug release testing of medicated chewing gums☆

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Abstract

An apparatus was specially designed and constructed for release testing of medicated chewing gums. The adjustable instrumental settings such as temperature, chewing frequency, chewing time, volume of test medium, distance between the jaws and twisting angle increased the versatility of the apparatus. Selection of the test medium was also an important parameter. Each sample was kneaded mechanically in separate test chambers and the drug release was followed by sampling and HPLC analysis. Different gum formulations were tested and the obtained results demonstrated satisfactory release curves for a variety of formulations and active ingredients. The tested gum formulations comprised nicotine, meclizine, dimenhydrinate and xylitol. The apparatus proved to be suitable in product control of commercial batches but also a useful tool in the research and development of medicated gum formulations.

Keywords: Drug release testing in vitro; Medicated gums; Equipment for gum formulations; Nicotine; Meclizine; Dimenhydrinate; Xylitol

1. Introduction

In vitro drug release testing of drug formulations is well established for different types of pharmaceutical dosage forms. Suitable tests are carried out to demonstrate the appropriate release of one or several active ingredients. In particular, dissolution testing is required for all solid oral pharmacopeial dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect [1]. The existence of official standards and settings are therefore helpful guidelines in this field [1,2]. Standardized equipment for disintegration, dissolution and drug release testing are available on the market. These apparatuses are however not suitable for release testing of chewing gums since gum formu-

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lations may have water insoluble and non-disintegrating matrices that differ from those used in traditional solid oral dosage forms. Hence, a gum formulation behaves differently and mastication is needed for the release of the drug compound. At present time only few publications refer to devices that simulate the human mastication of chewing gums; one apparatus is described by Christrup and Moeller [3] and the evaluation of another equipment was presented some years ago [4].

Pharmacia and Upjohn has been involved in the research and development of medicated chewing gums for many years, and the first equipment for drug release was developed for more than 10 years ago. The aim has been to develop a test equipment specific for gum formulations that continuously exposes the interior of the chewing gum, in order to permit contact between drug and the surrounding medium. To release the active ingredient(s) a mechanical treatment of the chewing gum is required, for example by using an instrumental mastication process that simulates the normal chewing [5–8]. During the last years improvements have been made in order to maximise the versatility. Thus the apparatus has now easily adjustable settings of temperature, chewing frequency, chewing time, volume of medium, distance between the jaws and twisting movement [9]. The purpose of this study was to demonstrate that this specially designed and constructed equipment may be suitable as universal test equipment for medicated chewing gums.

2. Experimental

2.1. Chemicals

The following chewing gum formulations with active drug substances and chemicals were used, Nicorette® Classic, 2 mg nicotine as nicotine polacrilex (Pharmacia and Upjohn); Nicotinell®, 2 mg nicotine as nicotine polacrilin (Novartis); Travvell®, 20 mg dimenhydrinate (Asta Medica); Experimental chewing gum formulation, 25 mg meclizine hydrochloride; V6®, 40 mg xylitol (Fertin).

All chemicals and solvents were of pro analysi or HPLC grade quality.

Potassium phosphate, monobasic, di-sodium hydrogen phosphate 2-hydrate, *ortho*-phosphoric acid 85%, methanol, acetonitrile 99.9%, n-heptane 95%, tetrabutyl ammonium bromide 99%, sodium dodecyl sulphate. The water used was of Milli-Q quality.

Nicotine hydrogen tartrate and dimenhydrinate were purchased from Sigma, and xylitol from Xyrofin, Finland. Test media for the release experiments consisted of pure water (gum containing dimenhydrinate), water–sodium dodecyl sulphate (99.9:0.1) for gum formulations containing nicotine or xylitol, and for meclizine gum a solution of sulphuric acid (0.05 M).

Mobile phases, specified in Section 2.2.2 and Table 1 were filtered and degassed before use.

2.2. Instrumentation

2.2.1. Drug release equipment

A chewing apparatus was used for simultaneous testing of six individual samples. The design and function of each test chamber has been presented in [9]. An essential detail is the fully transparent wall of the vessel, a construction made in order to permit visual inspections during the test runs. The test vessel consists of several components, jacketed and transparent glass chamber; upper and lower jaws; setting of twisting angle; position of the chewing gum and the supporting nylon net; circulation of thermostat controlled water. The instrumental settings are easily adjustable to suit different gum formulations but the following settings and conditions were used as default values in the present study if not specified otherwise, temperature of the test medium, 37°C; volume of test the medium, 40 ml; chewing frequency, 40 strokes min^{-1}; distance between the upper and lower jaws, 1.6 mm; twisting angle, 20° and total chewing time, 45 min.

Aliquots of 0.5 ml were withdrawn from each test cell at different time points during the in vitro testing procedure. The samples were transferred to HPLC vials and centrifuged prior to HPLC analysis.

Table 1
Summary of used conditions for tested products, release equipment and chromatography

Product	Release equipment settings		Chromatography settings	
Nicorette® Classic 2 mg nicotine (Pharmacia and Upjohn)	Test medium	Water–sodium dodecyl sulphate (99.9:0.1)	Mobile phase	0.08 M Phosphate buffer pH 6.5/methanol (40:60)
	Volume of the test medium (ml)	40	Column	Genesis C18, 100 × 4.6 mm, 4 μm, sorbent AB
	Temperature of the test medium (°C)	37	Injection volume (μl)	10
	Chewing frequency:	40	Flow rate (ml min^{-1})	1.0
	Distance between upper and lower jaws (mm)	1.6	Detector	UV
	Twisting angle (°)	20	Wavelength (nm)	260
	Chewing time (min)	45		
Nicotinell® 2 mg nicotine (Novartis)	Test medium	Water–sodium dodecyl sulphate (99.9:0.1)	Mobile phase	0.08 M Phosphate buffer pH 6.5/methanol (40:60)
	Volume of the test medium (ml)	40	Column	Genesis C18, 100 × 4.6 mm, 4 μm, sorbent AB
	Temperature of the test medium (°C)	37	Injection volume (μl)	10
	Chewing frequency:	40	Flow rate (ml min^{-1})	1.0
	Distance between upper and lower jaws (mm)	1.6	Detector	UV
	Twisting angle (°)	20	Wavelength (nm)	260
	Chewing time (min)	45		
Experimental chewing gum, 25 mg meclizine hydrochloride	Test medium	0.05 M Sulphuric acid	Mobile phase	0.1 M Phosphate buffer pH 2.5/acetonitrile (30:70)
	Volume of the test medium (ml)	40	Column	Nucleocil C18, 250 × 4.6 mm, 5 μm, hicrom
	Temperature of the test medium (°C)	37	Injection volume (μl)	20
	Chewing frequency:	40	Flow rate (ml min^{-1})	1.3
	Distance between upper and lower jaws (mm)	1.8	Detector	UV
	Twisting angle (°)	20	Wavelength (nm)	230
	Chewing time (min)	45		
Travvell® 20 mg dimenhydrinate (Asta Medica)	Test medium	Water	Mobile phase	0.05 M Phosphate buffer pH 3.0/acetonitrile 80:20
	Volume of the test medium (ml)	40	Column	Nova-Pak C18, 100 × 5 mm, 4 μm, waters
	Temperature of the test medium (°C)	37	Injection volume (μl)	15
	Chewing frequency:	40	Flow rate (ml min^{-1})	1.0
	Distance between upper and lower jaws (mm)	1.8	Detector	UV

Table 1 (*Continued*)

Product	Release equipment settings		Chromatography settings	
	Twisting angle (°)	20	Wavelength (nm)	285
	Chewing time (min)	60		
V6® 40 mg xylitol, Fertin	Test medium	Water–sodium dodecyl sulphate (99.9:0.1)	Mobile phase	Acetonitrile/water (75:25)
	Volume of the test medium (ml)	40	Column:	μ-Bondapak NH_2, 300 × 3.9 mm, 10 μm, waters
	Temperature of the test medium (°C)	37	Injection volume (μl)	10
	Chewing frequency	40	Flow rate (ml min^{-1})	1.0
	Distance between upper and lower jaws (mm)	1.6	Detector	Differential refractometer
	Twisting angle (°)	20	Wavelength (nm)	
	Chewing time (min)	45		

2.2.2. Chromatography

Waters HPLC systems were used for the chromatographic assays. The instruments were equipped with autosamplers and either UV-or a differential refractometer detector. The injected sample volume was generally 10 μl (nicotine, xylitol), except for dimenhydrinate and meclizine that required 15 and 20 μl, respectively.

Separation of the active ingredients were achieved by using the following conditions, see Table 1. As documented in this table it can be seen that each formulation requires different instrumental settings and conditions in order to obtain optimal results.

3. Results and discussion

3.1. Drug release equipment settings

A nicotine chewing gum, 2 mg, was used to demonstrate how selected instrumental settings affected the drug release profile. The results are presented in detail in [9].

The chewing frequency was set to 40 strokes min^{-1}. When the frequency was increased or decreased, the slope of the curve was almost unchanged. The released drug per stroke was basically independent of the chewing frequency.

The temperature of the test medium was set to 37°C, the normal temperature in the oral cavity of man. The release of the active ingredient was as expected, affected by temperature, a raise increased the released drug amount while a fall in temperature resulted in a decrease of the released amount of the drug.

The distance between the upper and lower jaws was set to 1.6 mm. The release of the active ingredient was also influenced by the distance between the jaws, an increased distance delayed the release of drug substance to reach the maximum (100% released drug substance) while the opposite resulted in an increased release of the drug amount at the same time period. However with increased chewing time, >45 min, this difference was levelled out.

3.2. Testing of medicated chewing gums

Gum formulations with different composition and medical purpose were used to demonstrate the versatility of the chewing apparatus. The gum formulations contained the following active ingredients, nicotine, meclizine, dimenhydrinate, and xylitol, respectively. The presented results are mean values $\pm$ S.D., of six observations.

Two nicotine gum formulations, supplied from different manufacturers, were studied. The active ingredient is used in smoking cessation and smoking reduction therapy. The obtained release profiles were very similar, see Fig. 1. The instrumental settings were identical for the two medicated

gums. Therefore, if the curves had been dissimilar, it is assumed that different matrix composition existed.

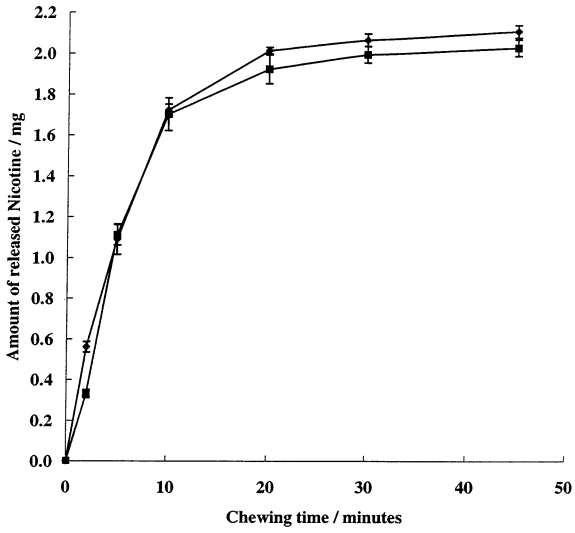

Fig. 1. Release of nicotine, expressed as milligram of label claim, from two different chewing gum formulations, Nicorette® 2 mg Classic and Nicotinell® 2 mg. Condition, Table 1. Key, Nicorette® 2 mg Classic (square), Nicotinell® 2 mg (diamond).

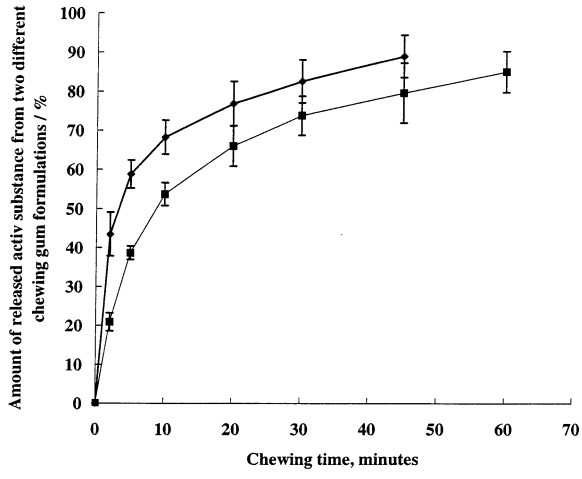

Fig. 2. Release from two different travel gum formulations containing 25 mg meclizine from an experimental chewing gum and 20 mg dimenhydrinate, Travvell®, expressed as percentage of label claim. Condition, Table 1. Key, Experimental chewing gum containing 25 mg meclizine (diamond), Travvell®, containing 20 mg dimenhydrinate (square).

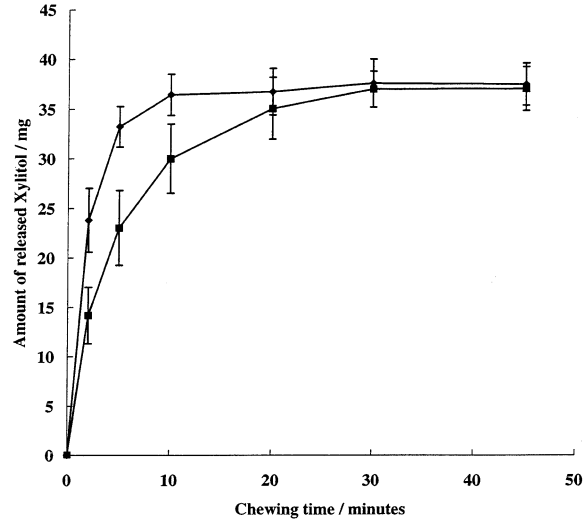

Fig. 3. Release of xylitol from a chewing gum, V6®, containing 40 mg of the active substance, expressed as mg of label claim, using two different settings of the distance between the jaws. Condition, Table 1. Key, 1.6 mm distance between the jaws (diamond), 2.0 mm distance between the jaws (square).

Another type of medicated chewing gums is used in the treatment of travel sickness. The active drug substance can be dimenhydrinate or meclizine. Obtained results are depicted in Fig. 2.

A chewing gum formulation containing xylitol was also tested, see Fig. 3. This ingredient is used in many sugar free products since it is not promoting dental caries. A shorter distance between the jaws increased the release rate of xylitol.

Besides the presented versatility in the instrumental settings there is another parameter to be considered, that of the test medium. The choice of test medium can be of crucial importance to reach the optimal test conditions for a specific chewing gum formulation. Three different test media were used in this study to suit each specific gum formulation, pure water (dimenhydrinate), a solution of diluted sulphuric acid (meclizine), see Fig. 2 and water containing a detergent (nicotine or xylitol), see Figs. 1 and 3. An aqueous fluid should in general be used as test medium. If possible, the pH should be in the neutral range, to mimic the pH of human saliva. The selection of medium should also be based on the physical–chemical characteristics of the drug. Pure water can be used

as test medium in certain cases, e.g. when the chewing gum contains buffering salts, but it should be noticed that factors as pH and surface tension of the test fluid can depend on the source of water or be changed during the dissolution test itself. It can be useful to add small amounts of a surfactant to reduce the surface tension of the test fluid and improve the solubility of the drug. The concentration of the surfactant should preferably be below its critical micelle formation concentration (CMC) but undesirable effects such as foaming during the chewing may still restrict the use of a number of surfactants. However, addition of sodium dodecyl sulphate in a concentration below CMC seems to be a good choice [10]. It is often favourable to use a buffered aqueous solution as test medium and a general recommendation is to use USP buffer solutions having pH-values in the range 4.5–8.0 [2]. However, higher or lower pH-values can in certain cases be selected, e.g. to obtain sufficient aqueous solubility of a poorly soluble compound with an amine function. In such a case, a medium consisting of a more basic or acid solution may be the best choice. In general, there is no need to degas the test medium since the frequent stroke and twisting process during the test run gives a thorough agitation of the test solution.

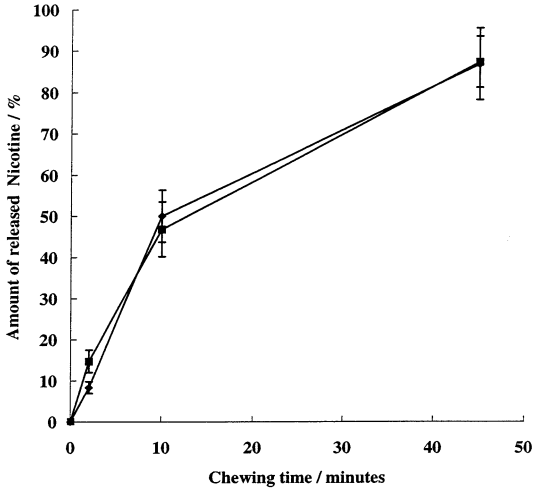

Fig. 4. Comparison between in vivo/in vitro release using Nicorette® 2 mg Classic chewing gum, expressed as percentage of label claim. Condition, see Section 3.2. The following settings were used — stroke frequency, 30 strokes min^{-1}, distance between the jaws, 1.8 mm. Key, in vivo release profile (square), in vitro release profile (diamond).

The in vitro results presented above are examples that show that the test apparatus can be used for quality control of commercial batches. Generally speaking, the in vitro test should distinguish between 'good' and 'bad' products/batches. Another field of use for drug release tests is to be found in the research and development of gum formulations. Since the chew out/in vitro comparison (instead of correlation) is not a regulatory requirement [10,11] it should be considered as an optional help during the development stage of new gum formulations. Drug release from a dosage form is an essential first step in drug absorption and bioavailability, the goal is to find a relationship between the in vitro results and the in vivo performance. There is a difficulty with dosage forms such as a chewing gum, the drug release is not only controlled by the dosage form, the user can to a considerable degree affect the release rate by his/her individual chewing behaviour.

In this study, nicotine chewing gums, Nicorette®, have been chewed in a strictly standardised way by a test panel. It consisted of a number of trained persons, and an average nicotine release curve was obtained, see Fig. 4. This curve was assumed to be a typical in vivo release curve for the actual nicotine chewing gum. Chewing gums from the same batch were also tested in the drug release equipment, and as depicted in Fig. 4. It was possible to document an in vitro profile very similar to that obtained by the chewing panel. Thus, the shown results indicate that an adequate in vivo/in vitro comparison should be obtainable with suitable settings of the drug release equipment.

4. Conclusions

The presented results have demonstrated the usefulness of an apparatus for release testing of gum formulations. Due to the adjustable instrumental settings and selection of the test medium, conditions can be created to meet the necessary requirements for each specific chewing gum.

The apparatus proved to be suitable in the quality control of manufacturing batches but also a useful tool in the research and development of medicated gum formulations.

Acknowledgements

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