European R&D Research & Development
Mundipharma Research

EXHIBIT B

The Effect of Ethanol on the *In-Vitro* Dissolution Rate of *Oxycodon – HCl* STADA® PR Tablets

Data Reference RPA Study Report 2007 -11 dated March 2007

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BACKGROUND

Some prolonged-release oral dosage forms contain drugs and excipients that exhibit a higher solubility in ethanolic solutions than water. Such products may be expected to exhibit a more rapid drug dissolution and release rate in the presence of alcohol.

The importance of alcohol testing of prolonged release formulations is in the focus of the authorities and corporations.

INTRODUCTION

Oxycodon – HCl STADA® is available in three dosage strength 20mg, 40mg and 80mg PR tablets.
Manufacturer:
STADA Arzneimittel AG
Stadastraße 2-18, 61118 Bad Vilbel

This report comprises general information e.g. appearance, ingredients and release mechanism but focuses on the effect of ethanol on the in-vitro dissolution rate of *Oxycodon – HCl* STADA® PR tablets respectively.

A) General information / description / photos

Oxycodon – HCl STADA® *PR Tablets: Ingredients*

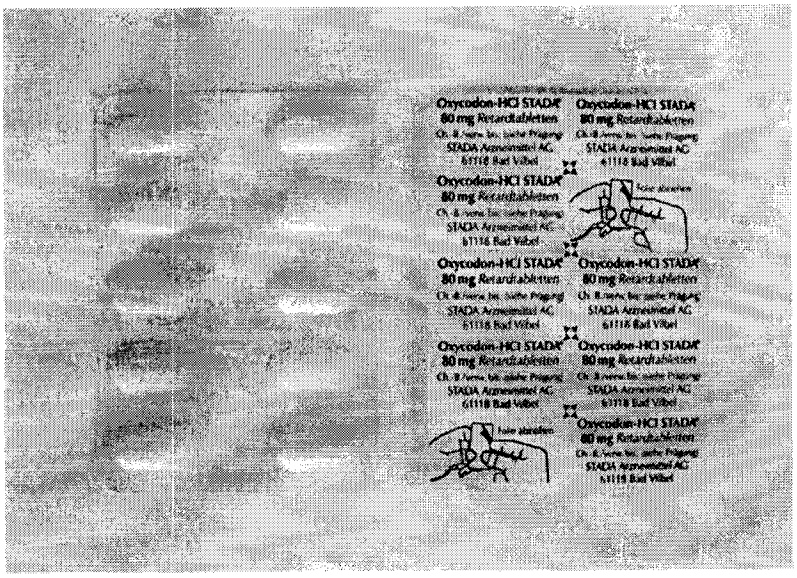
Active ingredient:
Oxycodone hydrochloride

Tablet cores:
Oxycodone hydrochloride
Macrogol 6000
Microcrystalline Cellulose
Ethyl Cellulose
Hyprolose
Hypromellose
Magnesium Stearate (Ph.Eur.)
Propylene Glycol
High disperse Siliciumdioxide
Talc
Sugar-Starch-Pellets (D-Glucose, Maize Starch, Sucrose)

Film coating:
Hypromellose
Titanium dioxide (E171)
Ferric (III)-hydroxid-oxide H_2O (E172)
Macrogol 6000
Talc

Oxycodon – HCl STADA® ***PR Tablets:*** *Packaging*

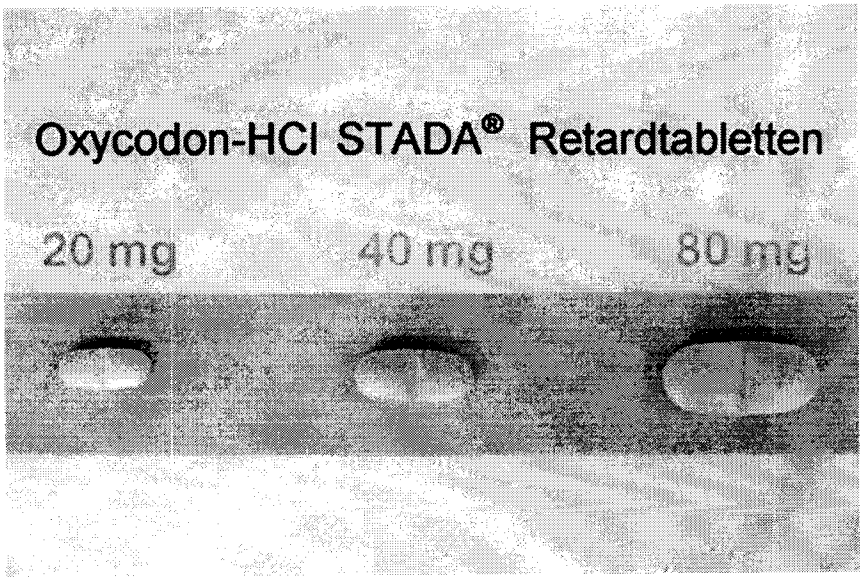
Example:



Oxycodone – HCl STADA® ***PR Tablets:*** *Dimensions*

	20mg	**40mg**	**80mg**
Colour	paly pink	paly orange	yellow - orange
Description	Bisect on two sides	Bisect on two sides	Bisect on two sides
Inscription	no	no	no
Weight (mg)	~128	~257	~512
Height (mm)	~3,2	~4,1	~4,9
Width (mm)	~4,6	~6,1	~8,1
Length (mm)	~10,1	~13,2	~17,2

Oxycodone – HCl STADA® ***PR Tablets:*** *Different strength*



B) The Effect of Ethanol on the *In-Vitro* Dissolution Rate of *Oxycodon – HCl* STADA® PR Tablets

MATERIAL

Oxycodon – HCl STADA® 20mg Retardtabletten
STADA Arzneimittel AG
Batch 0171

Oxycodon – HCl STADA® 40mg Retardtabletten
STADA Arzneimittel AG
Batch 0171

Oxycodon – HCl STADA® 80mg Retardtabletten
STADA Arzneimittel AG
Batch 0171

DESIGN OF EXPERIMENT

Dissolution was carried out using USP Apparatus 2 (basket Method) <711> at 100 rpm and 37°C in 500ml media.
Sampling time: 10, 30, 60 and 120 minutes

Sampled aliquots have been analysed by HPLC.

Dissolution media:
The in vitro experiment was using a dissolution media of USP Simulated Gastric Fluid (SGF) without pepsin and varying amounts of ethanol.

In this way, the drug product was subjected to specific quantities of ethanol to represent different types of alcoholic beverages in a person's stomach.

Amount of EtOH (% v/v) in the media (*dissolution performed in triplicate with one tablet / vessel and concentration each*):

	20% v/v EtOH
2% v/v EtOH	24% v/v EtOH
4% v/v EtOH	28% v/v EtOH
8% v/v EtOH	32% v/v EtOH
12% v/v EtOH	36% v/v EtOH
16% v/v EtOH	40% v/v EtOH

RESULTS of the dissolution studies in SGF (no pepsin) / Ethanol (various concentrations)

The results of the studies are presented in Table 1, 2 and 3 and shown graphically in Figure 1, 3 and 5 as dissolution profiles. Figure 2, 4 and 6 show percentage release versus concentration of ethanol at each timepoint. Figure 7, 8 and 9 show the summary of the 3 strengths, percentage release versus concentration of ethanol after 10 minutes, 1 hour and 2 hours.

A) Oxycodone – HCl STADA® 20mg PR tablets

Table 1 Oxycodone HCL dissolution rate in SGF / Ethanol for Oxycodone – HCl STADA® 20mg PR tablets

	Mean[1] Percent Dissolved			
ethanol (% v/v)	10 minutes	30 minutes	60 minutes	120 minutes
2	18,6	21,0	25,6	43,2
4	18,8	21,3	27,6	49,4
8	17,4	20,1	27,1	53,3
12	18,7	21,5	32,7	67,8
16	20,0	23,5	42,7	81,6
20	17,4	21,4	42,1	84,2
24	17,9	23,1	60,6	97,0
28	17,3	26,1	81,5	97,5
32	16,0	32,6	84,3	93,5
36	15,9	28,1	73,4	89,2
40	18,5	34,4	75,2	94,1

[1] Mean of 3 tablets

Figure 1 **Dissolution profiles of Oxycodone – HCl STADA® 20mg PR tablets in SGF / Ethanol**

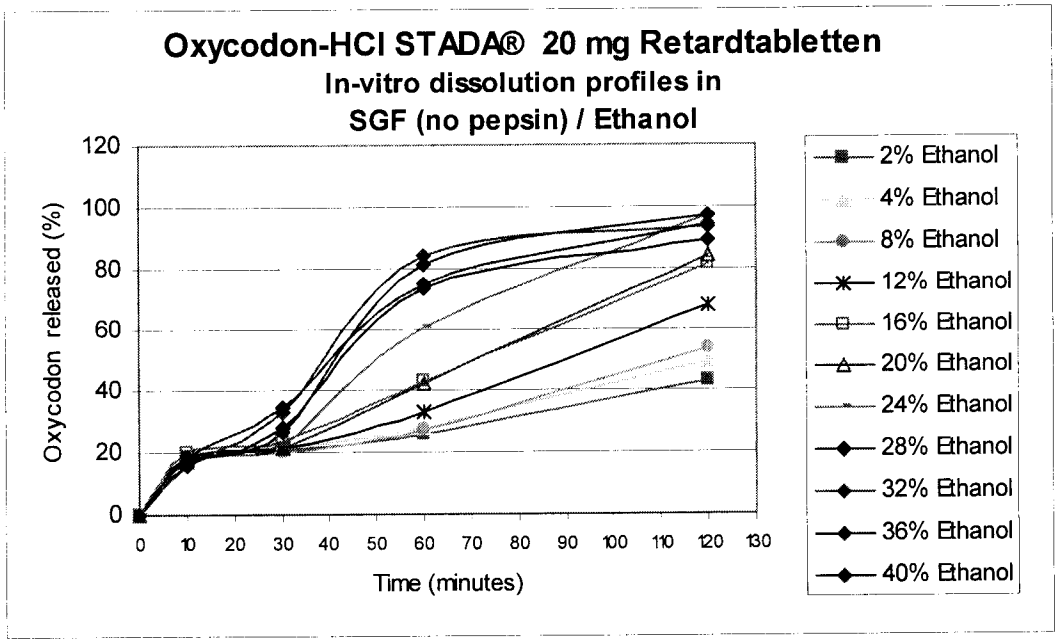
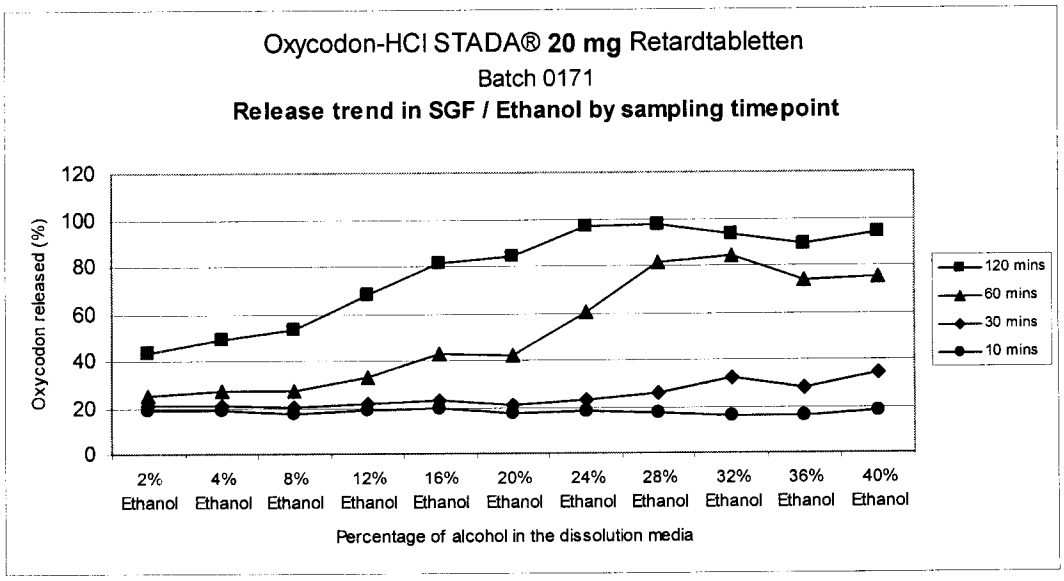


Figure 2 **Release trend of Oxycodone – HCL STADA® 20mg PR tablets in varying concentrations of ethanolic media by timepoint**



B) Oxycodone – HCl STADA® 40mg PR tablets

Table 2 **Oxycodone HCL dissolution rate in SGF / Ethanol for Oxycodone – HCl STADA® 40mg PR tablets**

	Mean[1)] Percent Dissolved			
ethanol (% v/v)	10 minutes	30 minutes	60 minutes	120 minutes
2	18,4	20,0	22,7	41,6
4	18,6	20,6	24,0	47,0
8	18,6	20,5	24,8	56,2
12	18,1	20,4	27,1	65,9
16	18,7	21,3	33,0	78,3
20	18,0	21,3	43,1	85,8
24	18,4	23,1	61,2	94,9
28	18,3	26,6	84,8	101,4
32	18,1	41,0	93,1	102,1
36	17,5	31,4	76,3	92,5
40	17,9	38,6	77,7	93,1

1) Mean of 3 tablets

Figure 3 **Dissolution profiles of Oxycodon – HCl STADA® 40mg PR tablets in SGF / Ethanol**

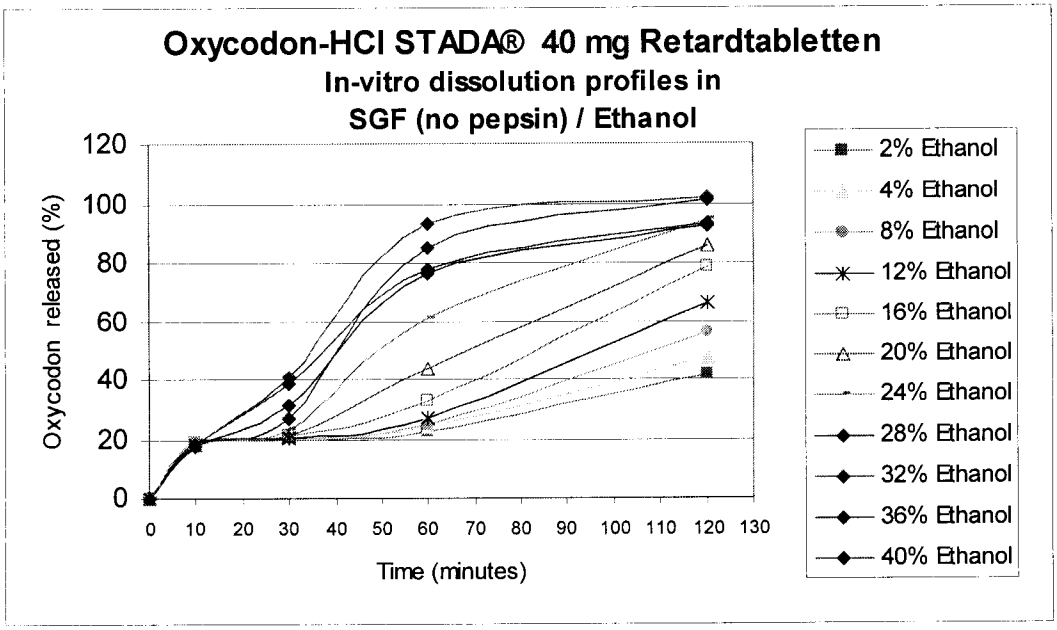
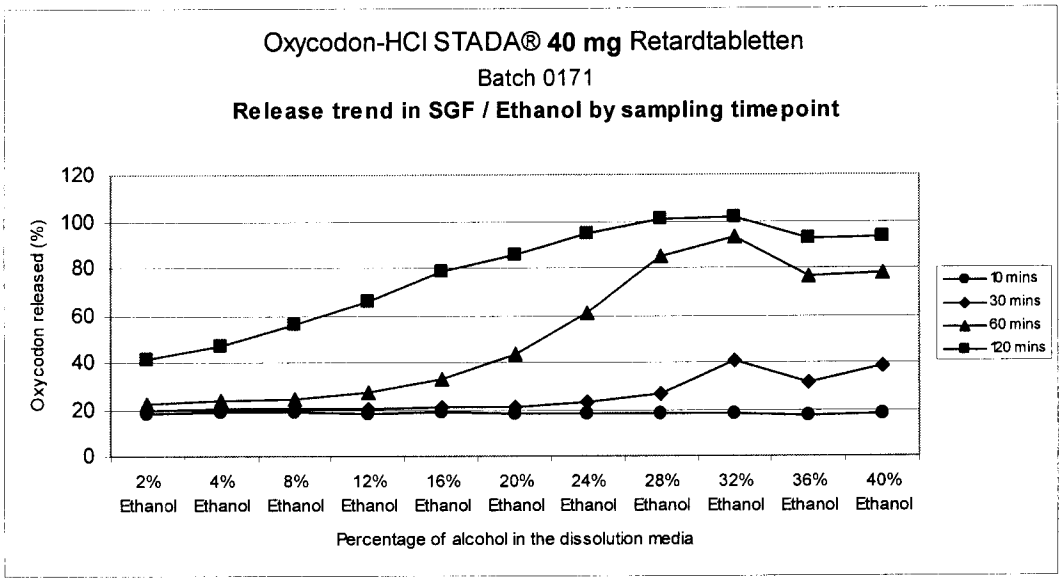


Figure 4 Release trend of Oxycodone – HCl STADA® 40mg PR tablets in varying concentrations of ethanolic media by timepoint



C) Oxycodone – HCL STADA® 80mg PR tablets

Table 3 Oxycodone HCL dissolution rate in SGF / Ethanol for Oxycodon – HCl STADA® 80mg PR tablets

	Mean[1] Percent Dissolved			
ethanol (% v/v)	10 minutes	30 minutes	60 minutes	120 minutes
2	18,7	19,9	22,7	43,1
4	18,7	20,0	23,0	46,7
8	18,8	20,2	24,8	56,8
12	19,2	20,9	28,5	69,4
16	18,2	20,0	32,6	77,0
20	17,6	21,3	47,1	85,2
24	18,5	25,3	65,0	94,7
28	18,6	33,1	84,6	98,4
32	18,3	50,7	89,2	94,8
36	18,4	37,2	77,4	93,9
40	19,6	43,4	79,5	94,1

[1] Mean of 3 tablets

Figure 5 Dissolution profiles of Oxycodone HCl STADA® 80mg PR tablets in SGF / Ethanol

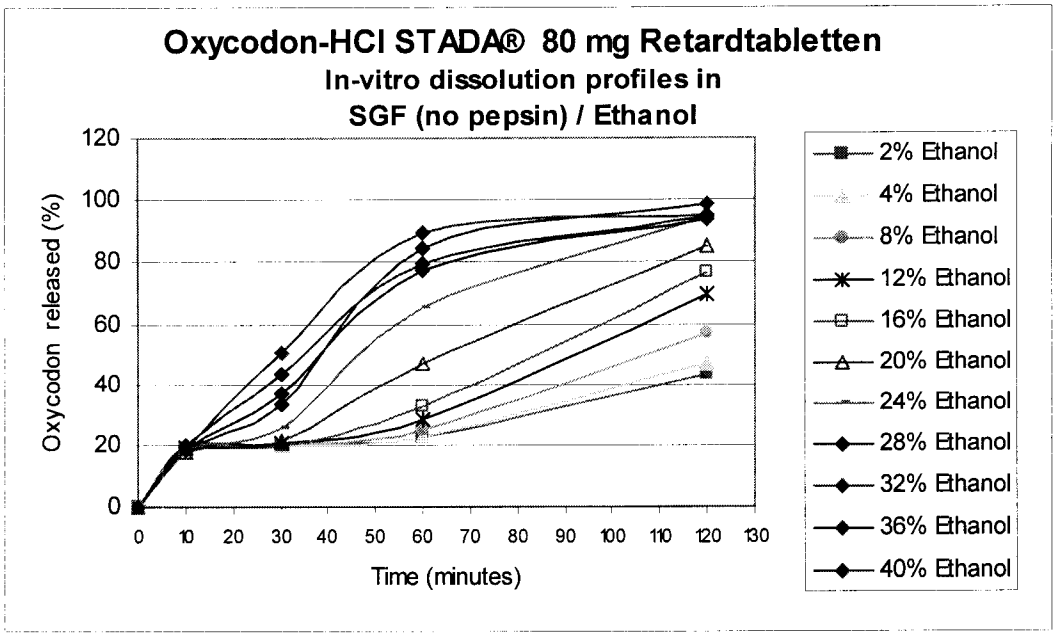
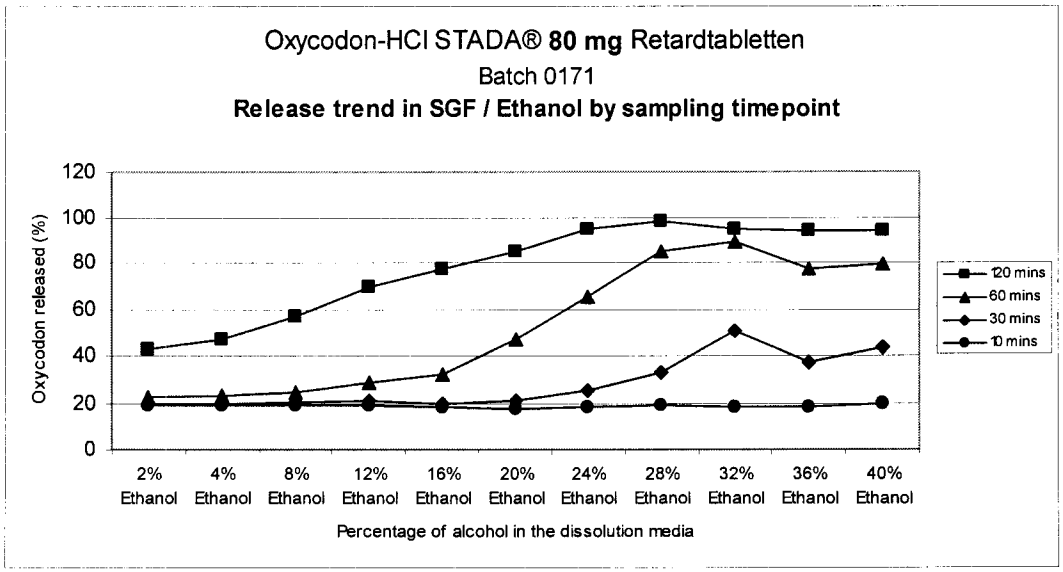


Figure 6 Release trend of Oxycodon – HCl STADA® 80mg PR tablets in varying concentrations of ethanolic media by timepoint



D) Summary of the strength

Figure 7 **Release trend of Oxycodon – HCl STADA® 20mg, 40mg and 80mg PR tablets in varying concentrations of ethanolic media after 10 minutes**

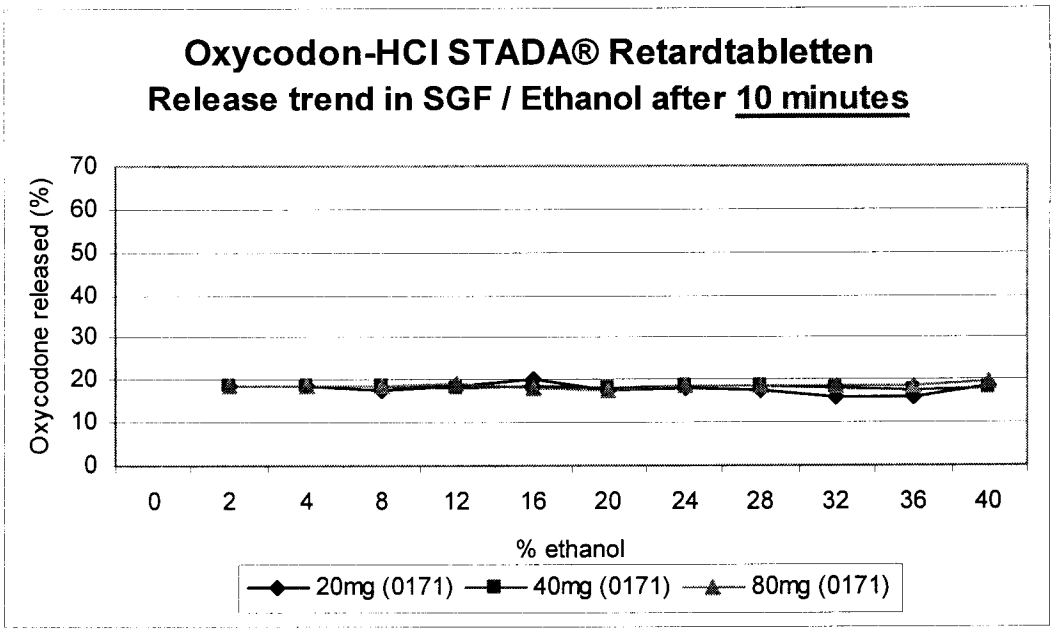


Figure 8 **Release trend of Oxycodon – HCl STADA® 20mg, 40mg and 80mg PR tablets in varying concentrations of ethanolic media after 1 hour**

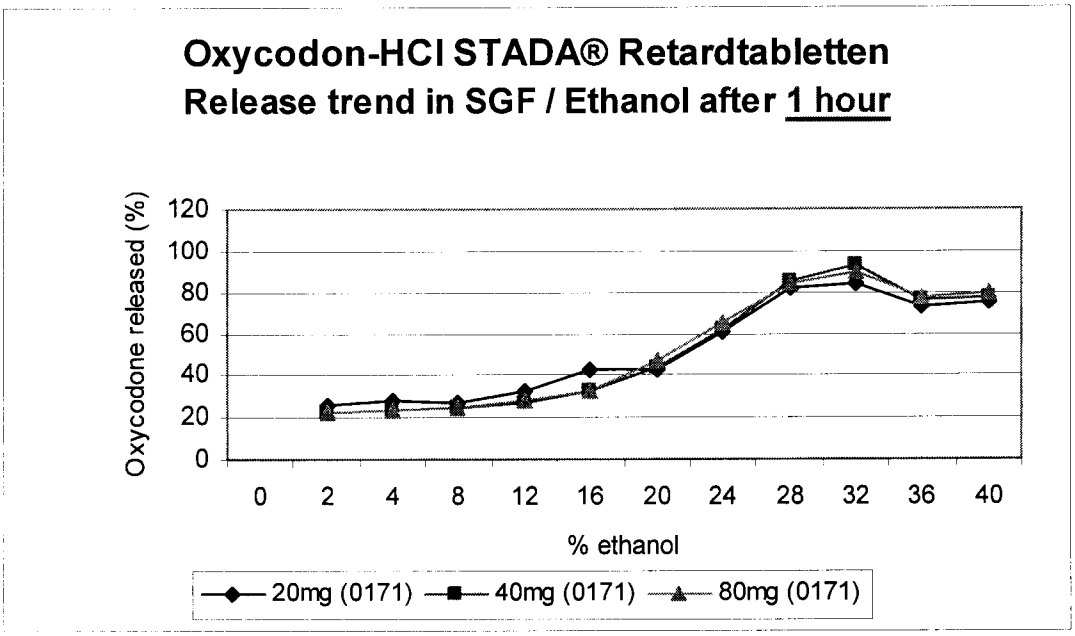
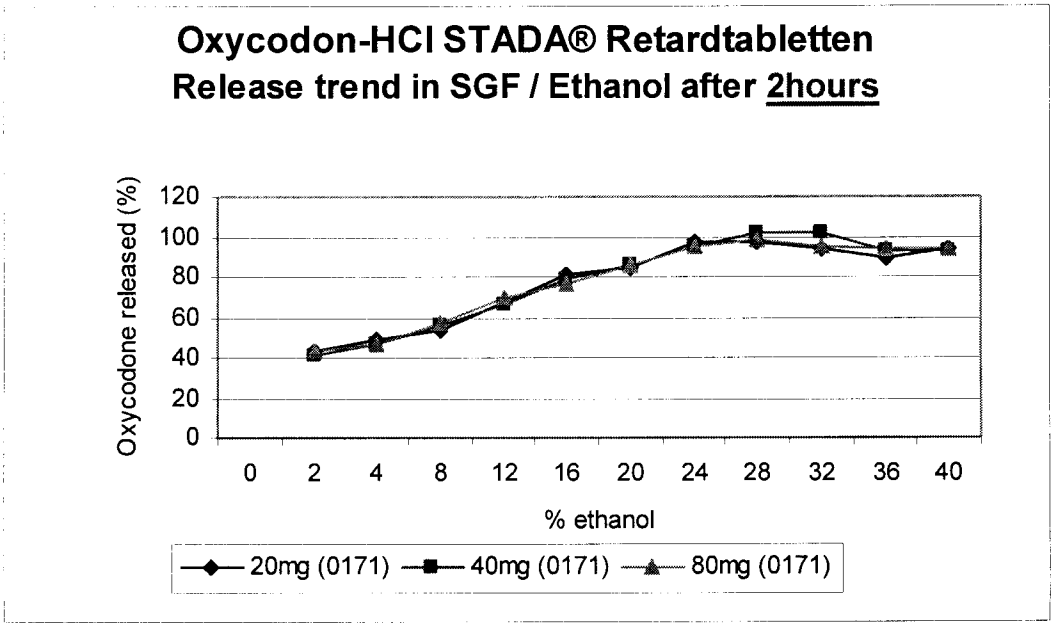


Figure 9 **Release trend of Oxycodon – HCl STADA® 20mg, 40mg and 80mg PR tablets in varying concentrations of ethanolic media after 2 hours**



CONCLUSION

"The results show an clearly impact of ethanol on the dissolution profile of *Oxycodon – HCl STADA® PR tablets."*