Programme no: 96

Abstract:

Dissolution or in-vitro drug release study is helpful in preliminary stages of formulation development and also used as quality control tool to study any batch to batch variations of marketed products. Pramipexole pamoate salt have 30 times less solubility in 6.8 pH buffer solution as compared to pramipexole. In present work dissolution profile of pramipexole and pramipexole pamoate was evaluated by using the USP paddle method as well as with the flow through cell (USP-4 apparatus) system. In USP-2 apparatus, sample was kept inside dialysis bag and in USP-4 apparatus, 2 ml flow rate was used with open mode. The dissolution profile was compared and in case of USP paddle apparatus, the amount of drug released in pramipexole was 80 % in 1 hour, whereas in pramipexole pamoate, 80 % of drug was released within 24 hours. Similarly, in USP flow through cell system, 80-90 % of drug was released within 10 minutes in pramipexole and in pramipexole pamoate, 80 % of drug was released within 2-3 hours. The obtained dissolution data were analyzed using different kinetic models as well as difference (f_1) and similarity (f_2) factors, also dissolution comparison was done using both powdered sample and suspension. The dissolution results shows that dissolution was retarded in pramipexole pamoate salt as that of pramipexole and hence, pramipexole pamoate can be further developed as a long acting formulation.

Comparative in-vitro dissolution study of Pramipexole and Pramipexole pamoate by using USP paddle method and the flow through cell system

Chaudhary Komal[1], Mehta Priti[1], Shah Sandeep[2], Dharmadhikari Shantanu[2]

[1]Institute of Pharmacy, Nirma University, Ahmedabad. Gujarat

[2]Erweka India Pvt. Ltd. Ahmedabad

13ftphdp21@nirmauni.ac.in

Introduction

- ⇒ **In vitro dissolution studies are an indispensable tool during several stages of pharmaceutical formulation development and provide critical information for quality control purpose to assess batch to batch variation, thus enabling evaluation of its stability and effectiveness.**
- ⇒ **In vitro drug dissolution data generated from dissolution testing can be related to in vivo pharmacokinetic data through in vitro-in vivo correlation (IVIVC).**
- ⇒ **Pramipexole is dopamine agonist and effective as monotherapy in early Parkinson's disease.**
- ⇒ **Pramipexole Pamoate is an additional salt of pramipexole prepared from pramipexole free base.**

Solubility of Pramipexole & Pramipexole pamoate salt

Sample	Media	Solubility in mg/ml
Pramipexole dihydrochloride	Phosphate buffer – 6.8 pH	> 200
Pramipexole free base		15.05
Pramipexole Pamoate		0.48

Pramipexole pamoate salt has been prepared with retarded solubility and in phosphate buffer –6.8 pH, solubility retarded by 30 times as compare to Pramipexole free base.

Sample preparation of suspension

Composition of vehicle : Carboxymethyl cellulose, Tween 80, Propylene glycol, Mannitol, water for injection, sodium hydroxide and hydrochloric acid for pH adjustment (6.8 pH)

89.5 mg of Pramipexole pamoate (Equivalent to 31.5 mg pramipexole)

↓

Added slowly into 1 ml of vehicle with constant stirring

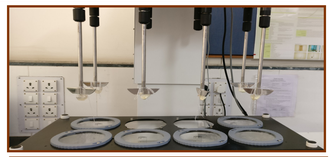
↓

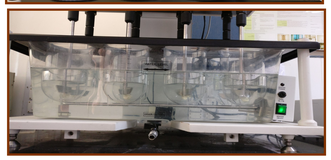
After uniform suspension get formed, make up suspension upto 2 ml with vehicle

(USP-2 apparatus)- USP Paddle method

Summary of Experimental Conditions

Dissolution Parameter	Test Conditions
Apparatus	USP apparatus 2 (Paddle)
Media	pH 6.8 Phosphate buffer
Media Temperature	37 °C± 0.2
Media Volume	300 mL
Paddle speed	25 rpm
Sample Introduction (Samples packed in activated dialysis membrane and tied with paddle)	Powdered sample, 31.5 mg 7 days maximum dose Suspension, Salt equivalent to 31.5 mg pramipexole suspended in 2 mL vehicle
Volume collected	5 mL

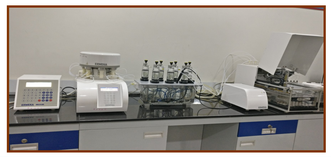




(USP-4 apparatus) Flow through cell method

Summary of Experimental Conditions

Dissolution Parameter	Test Conditions
Apparatus	USP apparatus 4 (Flow through cell)
Media and Media Temperature	pH 6.8 Phosphate buffer, 37 °C± 0.2
Assembly	22.6 mm tablet cell
Mode	Open mode
Sample Introduction	2 mL suspension (equivalent 31.5 mg 7 days maximum dose in vehicle)
Flow rate	2 mL/min
Volume collected	5 mL
Glass bead (1mm diameter)	13 gm (To maintain laminar flow)



Comparison of USP-2 v/s USP-4

USP-4 (Flow through

Time Points (mins)	% Cumulative Drug Release			
	Suspension		Powder	
	PRP Base	PRP Pamoate	PRP Base	PRP Pamoate
10	66.60	10.60	72.34	1.68
20	91.67	20.57	92.45	3.73
30	99.98	29.23	98.70	5.42
60	99.98	52.05	98.70	9.61
120	99.98	77.68	98.70	17.40
180	99.98	84.13	98.70	24.36
240	99.98	89.56	98.70	30.89
360	99.98	93.09	98.70	42.49
480	99.98	99.89	98.70	52.50

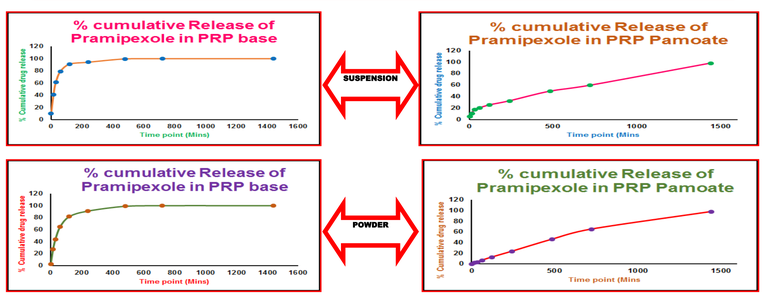
USP-2 (Paddle)

Time Points (mins)	% Cumulative Drug Release			
	Suspension		Powder	
	PRP Base	PRP Pamoate	PRP Base	PRP Pamoate
0	10.06	5.88	2.91	0.53
15	41.08	10.93	27.25	2.60
30	61.33	17.23	43.87	3.77
60	79.20	20.31	64.55	7.13
120	91.14	25.54	81.85	12.98
240	94.22	32.64	91.00	23.80
480	99.66	49.35	98.93	46.18
720	99.98	59.65	99.97	65.37
1440	99.99	98.13	99.97	98.13

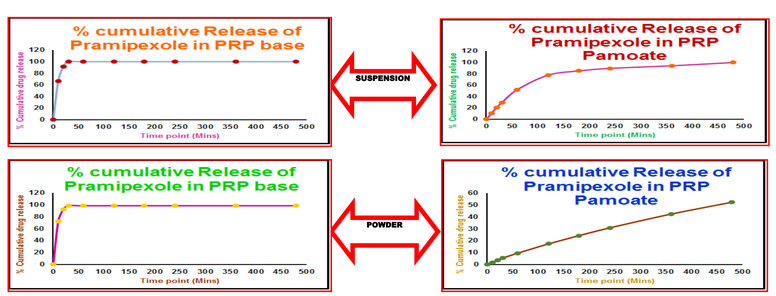
Different kinetic models for PRP Pamoate

	USP-2		USP-4	
	Model	R^2 value	Model	R^2 value
SUSPENSION	Zero order	0.986	Zero order	0.7404
	Higuchi	0.9785	Higuchi	0.8939
	First order	0.9010	First order	0.8827
	Korsemeyer-peppas	0.9792	Korsemeyer-peppas	0.9298
	Hixson Crowell	0.9581	Hixson Crowell	0.9045
POWDER	Zero order	0.9707	Zero order	0.9909
	Higuchi	0.9855	Higuchi	0.9866
	First order	0.9339	First order	0.9998
	Korsemeyer-peppas	0.9963	Korsemeyer-peppas	0.9967
	Hixson Crowell	0.9880	Hixson Crowell	0.8323

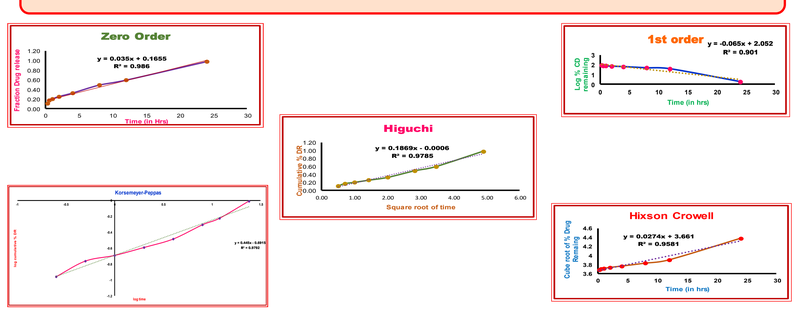
Release profile of PRP base & PRP pamoate by USP-2



Release profile of PRP base & PRP pamoate by USP-4



Representation of different kinetic models for PRP pamoate



Conclusion

- ⇒ Dissolution studies was performed by using USP paddle and flow through cell methods.
- ⇒ PRP Pamoate salt had retarded solubility as well as dissolution profile as compare to PRP base.
- ⇒ In-vitro release profile of salt suspension is better explained by USP paddle method as in case of injectable suspension no sink condition would be possible in the muscles.
- ⇒ By applying different kinetic models and while comparing R^2 value, it was concluded that salt suspension follows zero order kinetics by using USP-2 method, which is desirable for controlled release formulations.
- ⇒ Therefore, from dissolution profile and by comparing different kinetic models by using USP -4 and USP-2 methods that PRP pamoate has potential to further developed as a long acting depot formulation.

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