Formulation and Drug Release of Isoxsuprine HCL Enteric Coated Tablets

V. Nagamani

Department of chemical Technology, Osmania University, Hyderabad, India

Abstract— *The aim of the study is to formulate and evaluate enteric coated tablets using Isoxsuprine Hydrochloride as a model drug. Different core tablets and enteric coated tablets were prepared and drug release was studied. Isoxsuprine Hydrochloride core tablets were prepared by wet granulation method, using polymers, by changing drug ratios. The granules are evaluated for physical properties and the in-vitro drug release studies. Enteric coating was carried out using different sub coating materials. Enteric coating was performed in a mini coating pan at 107 rpm using low-pressure air atomized liquid spray technique. By changing the coating material, were done single coated, Double coated tablets are evaluated for uniformity hardness, friability, invitro disintegration and dissolution studies. The in-vitro drug release data was fitted into various kinetic models. All the formulations showed the values within the prescribed limit. It was observed that the higher rate and drug release was observed for the double coated tablets, this is because second layer having high viscosity.*

Keyword— Double coated tablets, disintegration and dissolution studies, Enteric coated tablets, formulations, Isoxsuprine Hydrochloride.

I. INTRODUCTION

Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the Gastrointestinal Tract (GIT) and the drug profile data, such as dose, absorption properties and the quantity of drug needed, one can determine the desired release rate of the drug from[1] controlled release dosage form. Drugs that are easily absorbed from the G.I.T and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem the oral controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time.Isoxsuprine, or Isoxsuprine hydrochloride, is a drug used as a vasodilator in humans and equines. Isoxsuprine is most commonly used to treat hoof-related problems in the horse.

Most commonly for laminitis and nonvascular disease, as its effects as a vasodilator are thought to increase circulation within the hoof to help counteract the problems associated with these conditions. Enteric coatings are those, which remain intact in the stomach, but they dissolve and release the contents once it reaches small intestine. Their prime intension is to delay the release of drugs, drugs sensitive to the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa. There are three reasons for putting such a coating on a tablet or capsule Ingredient to protect the stomach, to protect the drug from the stomach To release the drug after the stomach e.g. in the intestines. The drugs which most commonly cause stomach ulcers like aspirin, diclofenac and naproxen are frequently available with enteric coatings. Omeprazole, which is a drug which stops the stomach from producing acid, is itself broken down in acid and therefore the drug generally has an enteric coating around it either as a granule in the capsules or as a granule in the dispersible form. Sulfasalazine is used either for the treatment of arthritis or for the treatment of Corn's disease which is inflammation of the intestines. When used for arthritis it is very often given without an enteric coating so that it can be absorbed more quickly, whereas for Crowns' where it is needed in the intestines to work it is given with an enteric coating. It can be seen that an enteric coating is therefore there usually for a good reason and therefore such tablets or the contents of enteric coated capsules should never be crushed before being taken. To formulate and evaluate the Enteric coated tablets using Isoxsuprine Hydrochloride as a model drug by using different polymers, to evaluate the granules prepared from isoxsuprine Hcl for: Bulk density, Tapped density. Hausners ratio and cars index, to evaluate the prepared enteric coated tablets for: physical properties,Invitro drug release studies, Drug release mechanism[2.3].

II. MATERIALS AND METHODS

Table.1: Selected excipients for formulations

S.no	Name of the Ingredients	Category
1	Crosspovidone	Disintegrating agent
2	Crasscarmellos Sodium	Disintegrating agent
3	HPMC E15	Disintegrating agent
4	Carbapol	Disintegrating agent
5	PVPK30	Binder
6	Sodium carbonate	Alkalizing agent
7	Mannitol	Diluent
8	Magnesium Stearate	Lubricant
9	Talc	Glidant
10	Isopropyl alcohol	Solvent

Preparation of core tablets [4,5]:

The core tablets were prepared by wet granulation method. All the ingredients (show in Table 1), were mixed and passed through sieve no. 40 to get uniformally distributed and uniform sized particles. These granules are compressed on a single punching tablet machine. One batch of 20 tablets were prepared.

Preparation of enteric coated tablets:

The prepared core tablets were taken, for a single [2]coating process. It has two coatings, coated with cellulose acetate phthalate and HPMC .Required quantity of coating materials were added slowly to the vortex zone and the suspensions was mixed for 1hr.45 min.for single coated tablets and for double coated tablets was maintained without air bubbles then use the solution was used for coating[4]. The tablets were placed in a coating pan till the average weight as per the specifications (given in table 3).

Table.2: Selected Enteric Coated Materials

S.no	Name of ingredients	Category
	Sub coating	
1	HPMC	Sub coating materials
2	Cellulose acetate phthalate	Sub coating materials
3	Isopropyl alcohol	Solvent
	Enteric coating	
4	Meth acrylic acid	Enteric coating material
5	Titanium di oxide	Coloring agent

Table.3: Specifications of Sub coating

Inlet temp(^{o}c)	**60-65**
Out let temp(^{o}c)	**40-45**
Spray gun rpm	**2-3**
Air pressure(kg/cm^2)	**4-5**

Analytical method /Standard calibration of curve of Isoxsuprine

Hcl (pure drug) in suitable solvent

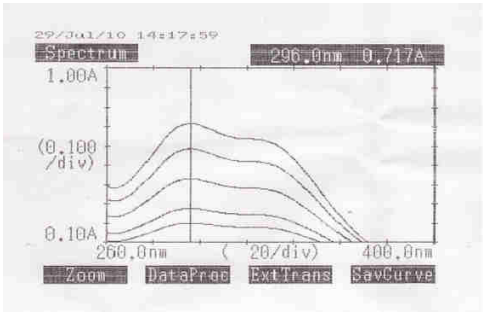
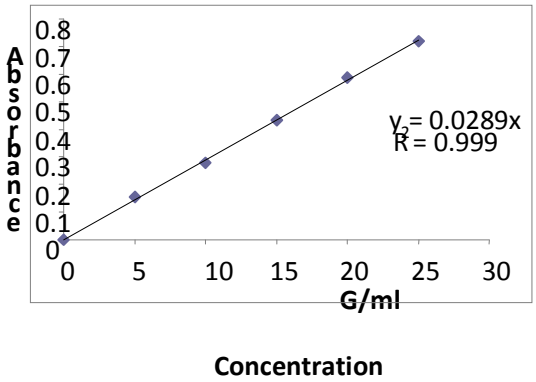


Fig.1: UV scanning image of pure Isoxsuprine hcl drug in solvent chloroform

Calibration curve for Isoxsuprine Hcl drug:



Cumulative analysis of Granules:

Table.4: Particle size of Granules

Granulates (wt%)	Mean thickness(µm)	Diameter of granules(µm)	Particle Size(µm)
3.0	52	30	0.0128
6.0	61	30	0.0226
9.0	75	30	0.0351
12.o	102	40	0.0425
15.o	110	40	0.0565
18.0	123	40	0.0638
Total weight=21.0	123	30	0.0772

Table.5: Pre compression properties of uncoated tablets

S.no	Formulation code	Bulk density	Tapped density	Carr's index (%)	Hauser's ratio (%)
1	F_1	0.472	0.509	7.27	1.079
2	F_2	0.374	0.398	6.03	1.064
3	F_3	0.398	0.425	6.26	1.066
4	F_4	0.404	0.432	6.48	1.069
5	F_5	0.472	0.509	7.27	1.079
6	F_6	0.447	0.481	7.07	1.075

Table. 6: Post compression properties of Isoxsuprine Hcl uncoated tablets:

S.no	Formulation code	Thickness (mm)	Diameter (mm)	Hardness(kg/cm^2)	Friability (%)	Weight variation (mg)
1	F_1	4.0±0.03	9.0	4.4	0.623	393±0.25
2	F_2	3.9±0.04	9.0	4.1	0.716	398±0.30
3	F_3	3.9±0.05	9.0	4.6	0.657	397±0.28
4	F_4	4.0±0.04	9.0	4.4	0.701	398±0.04
5	F_5	3.8±0.06	9.0	4.3	0.664	396±0.32
6	F_6	3.8±0.07	9.0	4.2	0.622	401±0.16

Table.7: Post compression properties of Isoxsuprine Hcl single coated tablets:

S.no	**Formulation code**	**Thickness (mm)**	**Diameter (mm)**	**Hardness (Kg/cm^2)**	**Friability test**
1	F_s	4.8±0.03	9.5	4.9	0.697
2	F_s	5.0±0.04	9.5	4.8	0.724
3	F_s	4.9±0.05	9.5	5.1	0.65
4	F_s	5.0±0.04	9.5	4.9	0.73
5	F_s	4.8±0.06	9.5	5.2	0.85
6	F_s	5.0±0.07	9.5	4.8	0.80
7	F_s	4.9±0.02	9.5	4.9	0.83
8	F_s	5.0±0.03	9.5	5.0	0.82

Table.8: Post compression properties of Isoxsuprine Hcl double coated tablets:

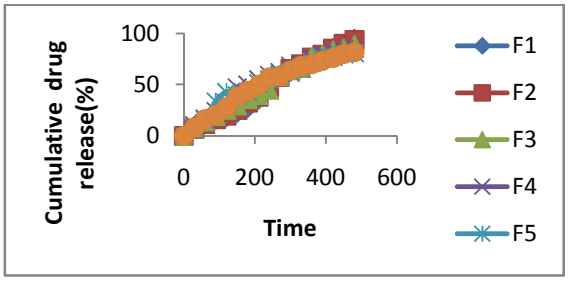
S.no	**Formulation code**	**Thickness (mm)**	**Diameter (mm)**	**Hardness (Kg/cm^2)**	**Friability test**
1	F_d	5±0.03	10.0	5.2	0.85
2	F_d	5.5±0.05	10.0	5.4	0.76
3	F_d	5.4±0.05	10.0	5.2	0.89
4	F_d	5.5±0.06	10.0	5.2	0.91
5	F_d	5.3±0.03	10.0	5.5	0.88
6	F_d	5.3±0.04	10.0	5.4	0.86
7	F_d	5.5±0.04	10.0	5.3	0.88
8	F_d	5.4±0.03	10.0	5.4	0.92

Table.9: In vitro studies of Isoxsuprine Hcl uncoated tablets

Time	Cumulative drug release (%)F_1	Cumulative drug release (%) F_2	Cumultive drug release(%) F_3	Cumultive drug release(%)F_4	Cumultive drug release(%)F_5	Cumultive drug release(%)F_6
0	0	0	0	0	0	0
30	9.9	7.1	8.1	10.25	7.65	8.21
60	12.5	11.6	14.0	16.6	15.3	16.25
90	15.8	16.5	19.5	23.8	33.3	20.25
120	18.4	19.8	25.3	31.9	42.3	27.9
150	22.8	25.3	29.7	47.05	39.06	38.3
180	27.1	32.5	36.04	49.6	42.7	43.8
210	35.4	38.2	39.6	54.8	50.85	49.4
240	47.89	47.1	45.0	59.03	54.8	56.92
270	58.99	57.5	58.2	61.8	59.6	58.2
300	62.8	65.3	64.05	68.04	61.5	63.7

330	69.3	69.6	66.3	70.25	65.9	63.7
360	72.57	76.5	76.7	75.6	71.3	69.9
390	78.4	79.01	79.0	79.21	75.8	73.1
420	85.2	85	83.5	81.3	77.2	75.9
450	89.6	89.9	85.2	84.5	79.6	79.8
480	94.5	93.4	88.9	85.3	80.6	81.5

In vivo drug release for all formulations:



Drug release of enteric coated tablets:

Table.10: Invitro drug release of single coated tablets

Time (min)	Cumulative drug release (%)F_s	Cumulative drug release (%)F_s	Cumulative drug release (%)F_s	Cumulative drug release (%)F_s
0	0	0	0	0
30	15.7	14.8	15.8	18.6
60	29.8	30.6	25.9	29.3
90	35.6	34.8	38.2	39.5
120	48.2	49.6	47.8	49.6
150	55.6	55.7	59.5	55.7
180	79.6	69.8	66.6	68.2
210	75.2	79.8	73.2	77.8
240	81.2	84.3	78.4	79.1
270	85.4	88.6	81.4	84.5
300	89.2	89.2	83.2	91.1
330	94.5	92.4	93.5	92.3

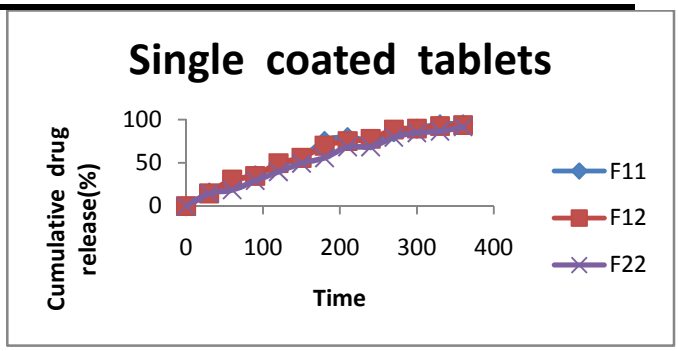


Table.11: Double coated tablets

Time(min)	Cumulative drug release F_d	Cumulative drug release F_d	Cumulative drug releaseF_d	Cumulative drug releaseF_d
0	0	0	0	0
30	28.6	29.8	34.8	36.9
60	41.5	45.9	45.9	48.4
90	58.4	57.3	51.6	53.4
120	63.5	67.8	59.4	58.9
150	83.4	71.3	69.7	59.8
180	88.9	79.3	78.7	63.8
210	92	81.3	79	63.8
240	93.2	86.8	80.6	79
270	94.8	89.8	82.4	82.1
300	94.8	92.6	85.3	90.5
330	95.8	94.5	86.9	92.3

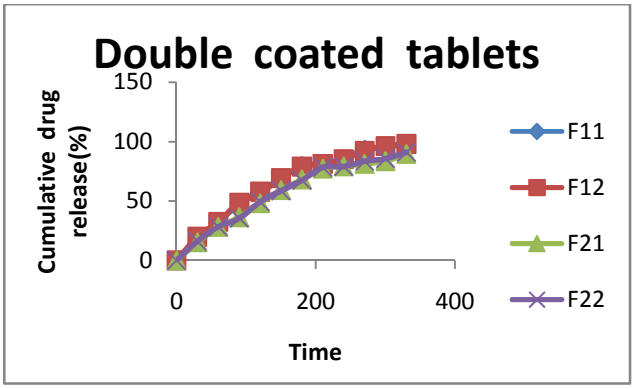


Table.12:The invitro disintegration studies for coated tablets

S.no	Single coated tablets	Disintegrating time
1	F_{S11}	3hrs
2	F_{S12}	2hr.30min
3	F_{S21}	2hrs
4	F_{S22}	2hr.30min

Table.13: Double coated tablets

S.no	Double coated tablets	Disintegrating time
1	F_{d11}	2hrs
2	F_{d12}	1.30min
3	F_{d21}	2hrs
4	F_{d22}	2hrs

III. CONCLUSIONS

From the present study we conclude that, amongst the all polymers studied,HPMC has shown has shown best drug release. Of the two coatings i.e. single coated, double coated tablets as shown best drug release. From the Disintegration and dissolution studies, it is observed that, in double coated tablets, drug will release faster than other coatings because the second layer is made up of high viscosity material.(because of coat thickness 5.5±0.05 and viscosity 4000cps).All the formulations are satisfactory with a proper disintegration time. In the case of uncoated tablets drug release is slower, where as in coated tablets drug release is observed to be faster. Enteric coated tablets are easily dissolved in the dissolution apparatus(it is at pH 6.8),hence will dissolve in Gastro intestinal tract which is also at pH 6.8.For Isoxsuprine hydrochloride coating is necessary, as it makes the unpleasant taste and gives a smooth finish.

REFERENCES

[1] Pharmaceutical dosage forms: Tablets Volume 3, Second Edition, Revised and expanded. Edited by; Herbert A. Lieberman, León Bachman, and Joseph B.schwartz.(No: 615.19 L62 p.).page no:651.
[2] Pharmaceutical dosage forms: Tablets Volume 1, Third Edition, Revised and expanded. Edited by; Herbert A. Lieberman, León Bachman, and Joseph B.schwartz.(L62 p.).page no: 302-311.
[3] International Journal of Drug Development & Research July-September 2011 | Vol. 3 | Issue 3 | ISSN 0975-9344 | Available online http://www.ijddr.in Covered in Official Product of Elsevier, The Netherlands 2010 IJDDR.
[4] Text book of pharmacy, Bentley&drivers.
[5] Rakesh,p.patel and A.M.suthan,Better control on Granulation,pharma development and technology 6(2),page pharmaceutical Granulation ensuring;2001,page.181-192.
[6] World intellectual property organization enteric coated tablets; 2002 pub No.WO/2005/051348,international filing.
[7] S.Bozdag, S.Calis and M. Summu. Formulation and stability evaluation of enteric coated omeprazole formulations 1. S.T.P.PHARMA SCIENCES.1999; 9:321-327.
[8] Sinha VR, Kumria Recoating polymers for colon specific drug delivery comparative in vitro evaluation. Act pharm. 2003; 53: 41-47
[9] Brunton LL, Lazio JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, New York, McGraw Hill, 2006.
[10] Summit Char borty, Sibaji Starker et al Formulation development and evaluation of pantoprazole enteric coated tablets. International journal of Chemtech Research 2009; 1:663:666
[11] Anroop B. Nair, Rachna Gupta, Formulation and evaluation of enteric coated tablets of proton pump inhibitor. Journal of basic and clinical pharmacy 2010; 001:215-264.
[12] Crotts G, Sheth A, Twist J, and Ghebre-Sellassi, worked from Pharmaceutical Research and Development, Pfizer Global Research and Development, NJ, Morris Plains, USA.Feb 10,2004.
[13] Singh Chatter studied on various polymers release rate. S.D. College of Pharmacy and Vocational Studies, Bhopal Road, Mujzaffarnagar.pg no:53-88.Dec,2005.
[14] S. N. Patel at all worked from Clinical Pharmacology unit, Christian medical college, Vellore, Tamilnadu., Sep7,2007.
[15] Vivek Kumar Unroll, Sreerama Krishna T, A Seetha Devi, KPR Chowdary.worked from Donbosco college of Pharmacy, Guntur, Andhra Pradesh, India, Hindu College of Pharmacy, Guntur, and Andhra Pradesh. May 24,2009.pg no:21-38.
[16]. International Journal of Pharmaceutical Sciences and Nanotechnology Volume 2 • Issue 1 • Jan 15, 2010.pg no: 111-202.
[17] Neuter Miyamura[a], Katsuji Uemura[a] and Masao Kobayashi[a] at all worked from Product & Technology Development Laboratory, Tanabe Seiyaku Co. Ltd., 16-89 Kashima-3-chrome, Yodogawa-ku, Osaka 532-8505,2011.
[18] Balky P, Basit AW. At all worked from Department of Pharmaceutics, The School of Pharmacy, and University of London, United Kingdom.2012.Recevied 18 September 2013.pg no:90-102.

[19] Michael D. Tousey at all worked from Thomas Engineering Shaklee, Pennwalt Stokes-Merrill, and Lasso. in 2014.Feb 22,pg no:321-432.

[20] Zhao N, Augsburg, LL Kurt A. Feely Institute of pharmaceutics and Biopharmaceutics, Heinrich-Henie universities Dussel dorf germany,http//dox.org/10.1016/j.epj.2011.02.03 DOI: nov,21, 2014.

.

.