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Development and Quality evaluation of sustained release pellets of eperisone HCl

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Abstract: The objective was to develop eperisone HCl sustained-release pellets through extrusion spheronization technique and to determine the influence of different hydrophobic (polymeric based and wax-based) and hydrophilic (polymeric based) matrix former on the release of eperisone HCl (BCS class I drug) and on pellet sphericity. The pellet formulations consisted of different hydrophobic and hydrophilic matrix formers like HPMC K4M (10-20%) HPMC K15M (10%), EC (7cps) (10-20%), Carnauba wax (10-20%), Compritol ATO 888 (10-20%), Glyceryl monostearate (10%), lactose and microcrystalline cellulose. The initial burst release of the drug from matrix pellet formulations was effectively controlled by coating with 5% EC (ethylcellulose) dispersion. The dissolution profile and drug release kinetics of coated pellet formulations were determined at both acidic and basic pH medium. SEM (Scanning electron microscope) technique was used to determine the surface morphology and cross-section of F5 and F7 pellet formulation. The mechanism of drug release of coated formulation followed non-Fickian diffusion. FTIR spectroscopy was conducted and no drug and excipients interaction was observed. The results had shown that optimized coated formulation was F5 and F7 which effectively extend the drug release for 12 hours.

Keywords: Eperisone Hydrochloride, sustained release, polymers, matrix formers, extrusion spheronization

INTRODUCTION

Eperisone hydrochloride is an anticholinergic agent which belongs to the antispasmodic class of drug. The molecular weight of Eperisone HCl is 295.801. It exhibits both vasodilator properties and skeletal muscle relaxant properties because it produces its action on vascular smooth muscles and within the central nervous system (Jain *et al.,* 2019, Ahmed *et al.,* 2020). It is commonly used in headache, cervical spondylosis and low back pain (Bose 1999, Beltrame *et al.,* 2008, Cabitza and Randelli 2008, Sertini 2008, Kunasekaran, Rajarajan *et al.,* 2012, Ahmed *et al.,* 2020). It produces its action by reducing the efferent activities of alpha and gamma, it also inhibits activities of the spinal cord by producing its action on the supra spinal structures and spinal cord and thus producing relaxant effects. Eperisone hydrochloride produces vasodilator activity which in turn enhances blood flow in muscles. No sedative effects have been reported yet that differ Eperisone HCl from other muscle relaxant agents. Its usual adult dose is 50 mg with a dosing frequency of three times a day. The biological half-life of Eperisone hydrochloride is from 1 to 4.3 hours (Mano and Miyaoka 1981, Bresolin *et al.,* 2009, Kunasekaran *et al.,* 2012, Ahmed *et al.,* 2020). Patient compliance with multiple dosing in a day is always problematic because it can result in missed dosing. Therefore, it is always preferable to select an extended release dosage regimen as it improves patient compliance because it has long duration of action as well as dosing frequency is also reduced which makes it more suitable therapy as the patient can easily follow this regimen (Nasiri *et al.,* 2016, Maboos *et al.,* 2018). Eperisone HCl can be formulated as ER (extended-release) dosage form because it has a short half-life and dosing frequency is three times a day (Jain *et al.,* 2019).

Designing an extended-release formulation of highly soluble drugs is always a challenge for scientists because of the risk of dose dumping, the non-linear release profile of drug, and burst release of the drug (Zeng 2004). The basic purpose for formulating SR (sustained-release) formulation is to avoid fluctuation of the drug in plasma over an extended period and to reduce the dosing intervals and side effects, which is due to plasma level fluctuations. The ideal candidate for extended-release dosage form is drugs that have shorter $t_{1/2}$ (Remington 2000). Pellets provide added advantage as multiple unit dosage forms i.e. there is rapid dispersion of pellets in the gastrointestinal tract which results in enhancement of absorption of the drug from the formulation and improves drug bioavailability, reduces fluctuations in peak plasma level of drug and reduces the dose dumping risk (Singh, *et al.,* 2007, Kranz *et al.,* 2009, Nasiri *et al.,* 2016, Maboos, *et al.,* 2018). There are several techniques for pellets manufacturing like extrusion spheronization, drug-layering technique, direct pelletization technique, and melt pelletization. For pelletization of lipids, the most commonly reported method is melt granulation (Hamdani,

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et al., 2003, Cheboyina *et al.,* 2004, Pongjanyakul, *et al.,* 2004, Cheboyina and Wyandt 2008, Roblegg *et al.,* 2011) but drug which is not heat stable it is not the preferred method for pelletization of lipid (Rahman *et al.,* 2009). The extrusion spheronization method is the most preferred method for the preparation of extended-release pellets. The most robust and reproducible technique which is reported for the pellets manufacturing is the extrusion spheronization method, pellets produce by this technique is spherical, having high density, low friable, good flow, and capacity of drug loading is high (Singh, *et al.,* 2007, Nasiri *et al.,* 2016, Maboos *et al.,* 2018).

GPS (Glyceryl palmitostearate), GMS (Glyceryl monostearate) and Compritol (Glyceryl behenate) are lipid glycerides, these form lipid matrices which are suitable for controlling drug release from formulations. They effectively retard the release of drugs in extended-release dosage forms. It has been reported that GMS serves as a spheronizing aid and inhibit the drug release from various extended-release formulations. It has been determined that stearates form an aggregate layer of lipid which is evenly distributed on the matrix former surface like HPMC and forms laminated microstructure moisture barrier because of interaction with a polymer (Jiménez, *et al.,* 2010). Glyceryl behenate is a mixture of different glycerols i.e. glycerol mono behenate, di behenate and tri behenate having low HLB value which indicates marked hydrophobicity (Hamdani *et al.,* 2003). Another type of lipid excipient is Carnauba wax, which also commonly used to retard the release of drug (Becker, *et al.,* 2015). The melting point of carnauba wax is high, it is hydrophobic in nature and when used in pellet formulation it forms its non-polar layer around pellets (Pozzi *et al.,* 1994, Nish *et al.,* 2012, Anepu *et al.,* 2015). The composition of Carnauba wax is 80-85% fatty esters, 3-6% acids, 10–15% free alcohols and 1-3% hydrocarbons (Dassanayake *et al.,* 2009). Polymer such as Ethyl cellulose forms hydrophobic inert matrix (Enayatifard, Saeedi *et al.,* 2009), it is extensively used as a carrier for extending the drug release in biomedical and pharmaceutical industries. Ethylcellulose is reported to have good biodegradability and biocompatibility when used alone or in combination with other polymers (Feng, *et al.,* 2013).

The aim of the current work was to prepare SR pellets of Eperisone HCl through extrusion and spheronization method, the pellets so produced, had compact structure and narrow particle size distribution.

MATERIALS AND METHODS

Materials

Eperisone HCl was provided by Platinum Pharma (Pakistan). Different polymers such as HPMC K4M, HPMC K15M, EC 7 cps, and EC 10 cps was provided by Colorcon® Limited. Plasticizer such as Triacetin USP was provided by Colorcon Limited. Talc was provided by BDH Laboratories Supplier. GMS, Compritol ATO 888 were provided by Gattefosse Foundation. CW was obtained from BDH laboratory suppliers.

Methods

Preparation of matrix pellets

Different Eperisone HCl pellet formulations were prepared as listed in table 1. The amount of drug in each pellet formulation was kept constant. The quantity of hydrophobic (polymeric based and wax-based) and hydrophilic (polymeric based) matrix former ranged from 10% to 20%. The drug and excipients were dispensed in quantity as mentioned in table 1. The lipids such as GMS and carnauba wax were pulverized in mortar and pestle. The dispensed quantity was blended and mix. The wet mass was then prepared by using distilled water (granulating fluid) in a planetary mixer except for the HPMC matrix-based formulation in which IPA was used as the granulating fluid. However, granulating fluid quantity was used appropriately for achieving the desired shape of pellets. The wetted mass was then processed into a mini screw extruder (Caleva Process Solution Ltd., UK). The mini screw extruder was fitted with a screen of 1 mm. The extruder was run at 55-65 rpm throughout the process. The cylindrical extrudates formed from the extruder were collected and then manually broken down into small cylinders in such a way that the length of the cylinders was equal to their diameter. The small cylinders were transferred into Spheronizer (Caleva Process Solution Ltd, UK). The spheronizer was run at 800 to 1000 rpm throughout the process. After completion of the spheronization process, the pellets were taken out and put in a hot air oven for drying at 40°C. The dried pellets were then passed through the sieve of an 18-24 mesh screen. The pellets were collected and evaluated for physicochemical properties, dissolution profile, image analysis, and drug release kinetics (Nasiri *et al.,* 2016 and 2019, Ansari *et al.,* 2020).

Sustained Release Coating

Trial formulations F1, F2, F3, F4, F5 and F7 were screened out for coating with 5% Ethyl cellulose dispersion. The ingredients, as mentioned in table 2, were dispensed and mixed in a homogenizer for about 10 minutes, however, agitation was continued throughout the coating process. The conventional coating pan was used for the coating process. The parameters that were set for coating process for 50 gram batch size of pellets were: pan speed = 40 r/min, nozzle diameter of spray gun = 1 mm, spray rate = 1 mL/min, inlet temperature =60–65◦C and spray pressure =40 psi. The weight gain after the completion of the coating process was about 5-7%. The formulation was then put in hot air oven for 2 hours at 40°C for drying (Nasiri *et al.,* 2016). The formulations were then taken out for evaluation of drug release profile.

Table 1: Composition of pellet formulations

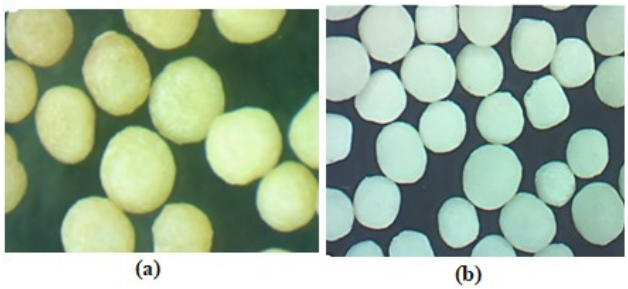
Formulation code	Drug (EPR)	Avicel pH- 101	Glyceryl Monostea-rate	Lactose DC	HPMC K4M	HPMC K15M	Compritol ATO 888	Carnauba Wax	EC (7cps)	Drug (EPR)	Avicel pH- 101	Glyceryl Monosterate	Lactose DC	HPMC K4M	HPMC K15M	Compritol ATO 888	Carnauba Wax	EC (7cps)	Total weight per capsule
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg/Cap)
F1	50	40	-	10	-	-	-	-	-	150	120	-	30	-	-	-	-	-	300
F2	50	40	10	-	-	-	-	-	-	150	120	30	-	-	-	-	-	-	300
F3	50	30	10	-	10	-	-	-	-	150	90	30	-	30	-	-	-	-	300
F4	50	30	10	-	-	-	10	-	-	150	90	30	-	-	-	30	-	-	300
F5	50	30	10	-	-	-	-	10	-	150	90	30	-	-	-	-	30	-	300
F6	50	30	10	-	-	10	-	-	-	150	90	30	-	-	30	-	-	-	300
F7	50	30	10	-	-	-	-	-	10	150	90	30	-	-	-	-	-	30	300
F8	50	20	10	-	10	-	10	-	-	150	60	30	-	30	-	30	-	-	300
F9	50	15	10	-	15	-	10	-	-	150	45	30	-	45	-	30	-	-	300
F10	50	10	10	-	20	-	10	-	-	150	30	30	-	60	-	30	-	-	300
F11	50	15	10	-	10	-	15	-	-	150	45	30	-	30	-	45	-	-	300
F12	50	10	10	-	15	-	15	-	-	150	30	30	-	45	-	45	-	-	300
F13	50	5	10	-	20	-	15	-	-	150	15	30	-	60	-	45	-	-	300
F14	50	10	10	-	10	-	20	-	-	150	30	30	-	30	-	60	-	-	300
F15	50	5	10	-	15	-	20	-	-	150	15	30	-	45	-	60	-	-	300
F16	50		10	-	20	-	20	-	-	150	-	30	-	60	-	60	-	-	300
F17	50	20	10	-	-	-	10	10	-	150	60	30	-	-	-	30	30	-	300
F18	50	15	10	-	-	-	10	15	-	150	45	30	-	-	-	30	45	-	300
F19	50	10	10	-	-	-	10	20	-	150	30	30	-	-	-	30	60	-	300
F20	50	15	10	-	-	-	15	10	-	150	45	30	-	-	-	45	30	-	300
F21	50	10	10	-	-	-	15	15	-	150	30	30	-	-	-	45	45	-	300
F22	50	5	10	-	-	-	15	20	-	150	15	30	-	-	-	45	60	-	300
F23	50	10	10	-	-	-	20	10	-	150	30	30	-	-	-	60	30	-	300
F24	50	5	10	-	-	-	20	15	-	150	15	30	-	-	-	60	45	-	300
F25	50		10	-	-	-	20	20	-	150		30	-	-	-	60	60	-	300
F26	50	20	10	-	-	-	10	-	10	150	60	30	-	-	-	30	-	30	300
F27	50	15	10	-	-	-	10	-	15	150	45	30	-	-	-	30	-	45	300
F28	50	10	10	-	-	-	10	-	20	150	30	30	-	-	-	30	-	60	300
F29	50	15	10	-	-	-	15	-	10	150	45	30	-	-	-	45	-	30	300
F30	50	10	10	-	-	-	15	-	15	150	30	30	-	-	-	45	-	45	300
F31	50	5	10	-	-	-	15	-	20	150	15	30	-	-	-	45	-	60	300
F32	50	10	10	-	-	-	20	-	10	150	30	30	-	-	-	60		30	300
F33	50	5	10	-	-	-	20	-	15	150	15	30	-	-	-	60		45	300
F34	50	-	10	-	-	-	20	-	20	150	-	30	-	-	-	60		60	300

Fourier transform infrared spectroscopy (FTIR)

FTIR technique was used for investigating any drug and excipient interaction in formulations (Nicolet-6700, Thermo ScientificTM, USA). The spectra at wave number ranging from 4000 to 1000 cm^{-1} were recorded for the drug and formulations (OMNICTM Specta Software).

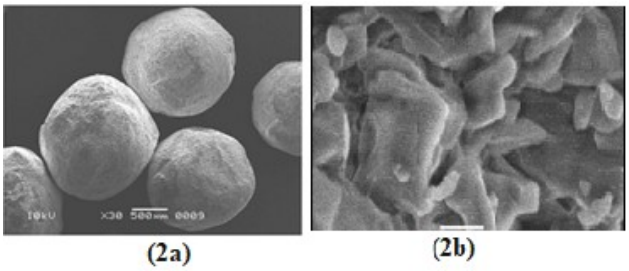
Table 2: Composition of Ethylcellulose 5% coating solution

Composition	Quantity
Ethyl Cellulose (EC-10cps)	5.0g
Triacetin USP/FCC	1.0g
Talc	1.0g
Isopropyl Alcohol	90 ml
Water	10 ml



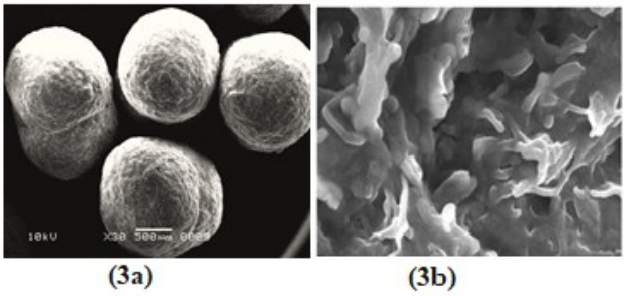
(a) (b)

Fig. 1: Stereo Micrographs of (a) EPR Matrix Uncoated Pellets (b) Ethyl Cellulose coated pellets



(2a) (2b)

Fig. 2: SEM surface images of EC coated pellets of Formulation F-5



(3a) (3b)

Fig. 3: SEM surface images of EC coated pellets of Formulation F-7

Flow properties

Hausner ratio, Carr's index, tapped density, bulk density and angle of repose were investigated for determination of flow property of each pellet formulation (Qazi *et al.,* 2013).

Friability

Friability of formulations was determined by putting 10 gm of pellets in the friabilator (Erweka GmbH D-63150, Husenstamm, Germany). The friabilator was run for 10 min at 25 rpm. The pellets were then collected from the friabilator and then passed through 250 µm mesh for removal of fines from pellets. The pellets friability were calculated by the below-mentioned formula (Dukić-Ott *et al.,* 2007).

$$\textit{Friability}\ (\%) = \frac{(\textit{Initial Weight} - \textit{Final Weight})}{\textit{Initial Weight}} \times 100$$

% friability should be < 1%.

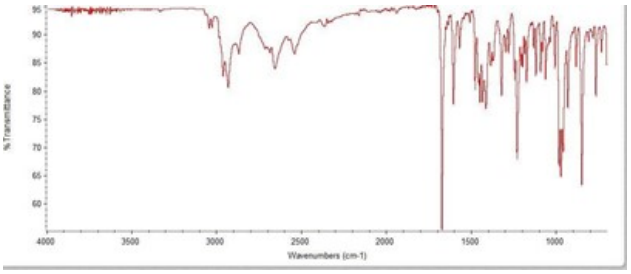


Fig. 4a: FTIR Spectra of Pure Eperisone HCl

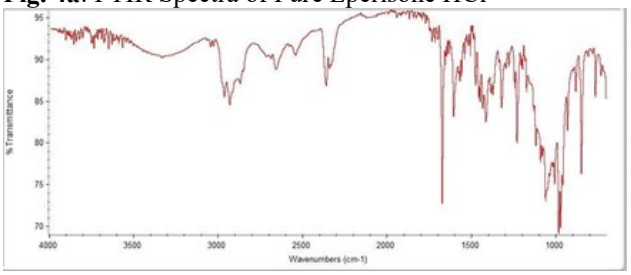


Fig. 4b: FTIR Spectra of Formulation F5

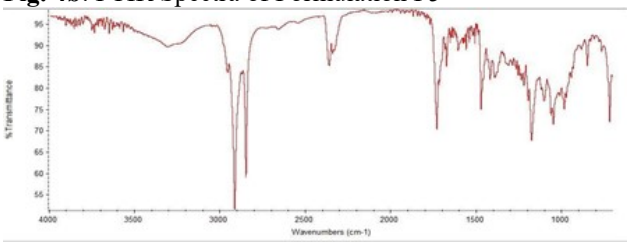


Fig. 4c: FTIR Spectra of Formulation F7

Assessment of pellet surface morphology

Image analysis

Stereomicroscope (Am Scope Digital, LED-1444A, USA) was used for the determination of pellet shape as well as area of pellets formulation (n=50). These images were taken into evaluation through image analysis software (NIH Image J 1.47v, USA) for measuring aspect ratio, sphericity, and Feret diameter. Sphericity determines the degree of roundness of particle (Chatlapalli and Rohera 1998, Sriamornsak *et al.,* 2008, Gowda *et al.,* 2009, Akhgari *et al.,* 2011, Gupta *et al.,* 2011). The formula for calculation of aspect ratio, sphericity is mentioned below:

$$\textit{Aspect ratio}\ (AR) = d_{max}/d_{min}$$

$$Sphericity\ (Shape\ Factor) = 4\pi A/P^2$$

Where,
A=area
P=perimeter
dmax=longest ferret diameter
dmin= shortest Feret diameters

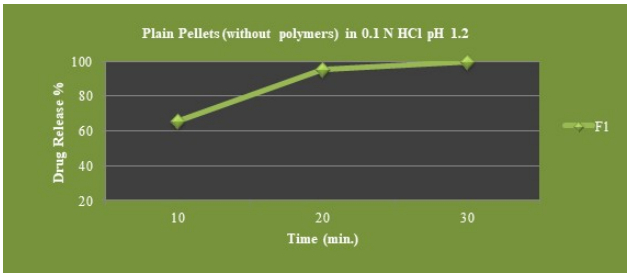


Fig. 5: *In-vitro* drug release profile of uncoated plain pellet F1 formulation

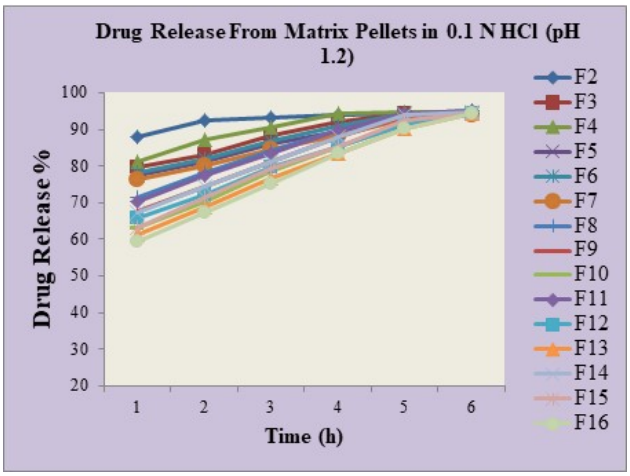


Fig. 6: *In-vitro* Drug release profile of uncoated matrix pellet formulations F2-F16 in 0.1 N HCl at pH 1.2

Scanning electron microscopy (SEM)

The external morphology of pellets and their cross-section was visualized through SEM (JSM-6380A, Jeol, Japan) at 10 kV by mounting the pellets on aluminium studs. The coating of aluminium studs was done with gold film through Auto Coater up to 300A and finally, the scanning under different magnification range i.e. 50 to 1500 times at accelerated voltage of 16 kV was performed and photomicrographs were obtained.

Drug content analysis

Twenty pellet-filled capsules from each formulation were taken and then weighed accurately in calibrated analytical balance. The pellets were then finely powdered by using mortar and pestle. The powder was weighed accurately in the proportion that contains 16.67 mg of Eperisone HCl. The weighed powder was then transferred to the volumetric flask of 100ml having sufficient double distilled water, which were then shaken to dissolve powder content and finally makeup 100 ml volume with double distilled water and then mixed for at least 15 minutes and finally sonicated for 15 minutes. After sonication, the solution was filtered and dilutions were made for obtaining the solution of 16.67µg/ml concentration for analysis. The obtained concentration samples were analyzed in a Double beam spectrophotometer at 260 nm wavelength (Double beam, UV-1800, Shimadzu, Japan).

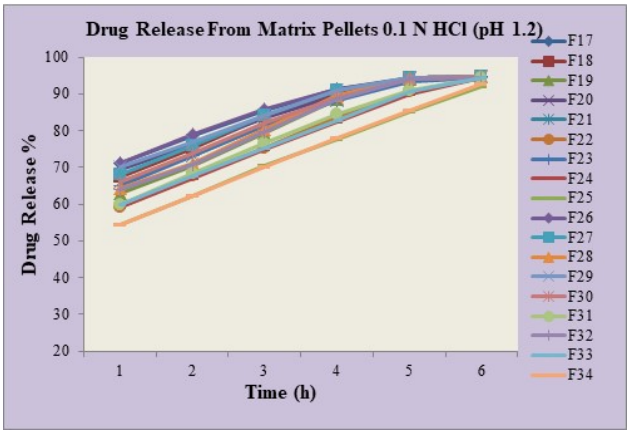


Fig. 7: *In-vitro* Drug release profile of uncoated matrix pellet formulation F17-F34 in 0.1N HCl at pH 1.2

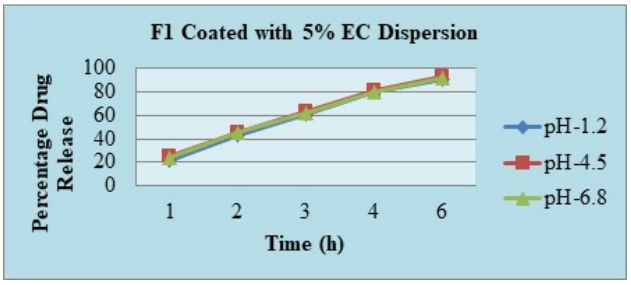


Fig. 8: *In-vitro* drug release profile of pellets formulation F1 coated with 5% Ethyl cellulose Dispersion

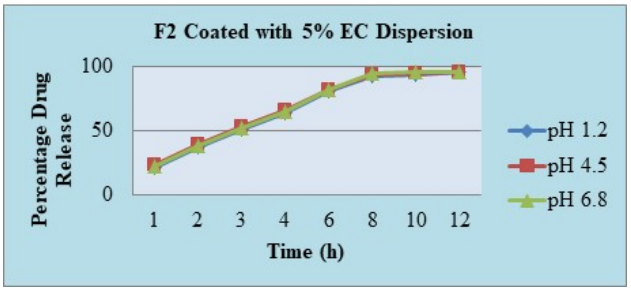


Fig. 9: *In-vitro* drug release profile of pellets formulation F2 coated with 5% Ethylcellulose Dispersion

In-vitro drug release study

Dissolution of uncoated pellet formulation was conducted in USP type-II paddle apparatus (Erweka, Heusenstamm, Germany) at pH 1.2, whereas, dissolution of the coated formulation was conducted at acidic and basic pH of dissolution medium i.e. pH 1.2 (0.1N HCl) pH 4.5 (phosphate buffer) and pH 6.8 (phosphate buffer) at 100

rpm. The volume of the dissolution medium was 900 ml. The temperature of the dissolution medium was maintained at 37°C±0.5°C throughout the test. The dissolution test was conducted for 12 hr. The sample volume after the pre-defined time intervals were withdrawn with the help of a graduated pipette and meanwhile replaced with the same fresh volume of dissolution medium. The withdrawal sample was then filtered and after suitable dilution was analyzed through spectrophotometer (Double beam, UV-1800, Shimadzu, Japan) at 260 nm.

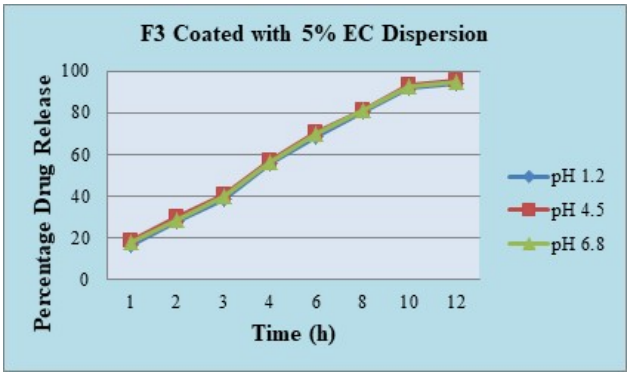


Fig. 10: *In-vitro* drug release profile of pellets formulation F3 coated with 5% Ethyl cellulose Dispersion

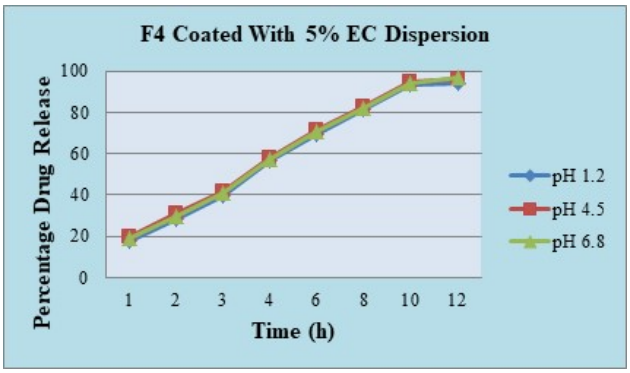


Fig. 11: *In-vitro* drug release profile of pellets formulation F4 coated with 5% Ethyl cellulose Dispersion

Drug release kinetic studies

The kinetics of coated formulation was determined by applying several kinetic models such as zero-order kinetics, Higuchi model kinetics, First-order kinetics, Korsmeyer Peppas model kinetics, Baker- Lonsdale model kinetics and Hixson-crowell model kinetics on data that was retrieved from dissolution studies by using DD Solver software.

Stability studies

Sustained-release F5 formulation was put in the amber colour bottle and stored for 6 months in the stability chamber and was subjected to accelerated conditions as per the recommended accelerated temperature and humidity conditions mentioned in ICH guidelines. Samples were drawn at 3 and 6 months for evaluation of the physical appearance of formulation, dissolution of drug and percentage drug content.

STATISTICAL ANALYSIS

The percentage drug release from formulations was calculated by using Microsoft Excel 2010. The shelf life of formulation F5 was determined through software Stab version 3.9.

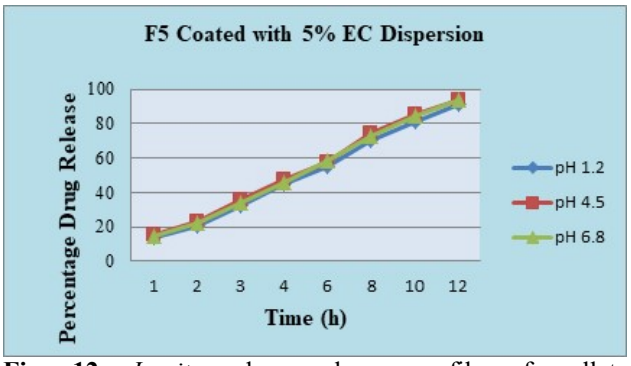


Fig. 12: *In-vitro* drug release profile of pellets formulation F5

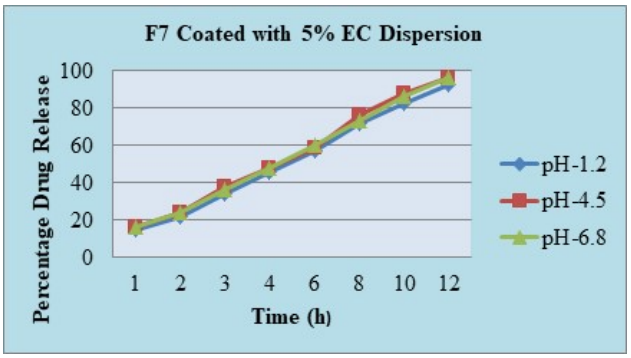


Fig. 13: *In-vitro* drug release profile of pellets formulation F7 coated with 5% Ethylcellulose Dispersion

RESULTS

Physical and chemical evaluation of uncoated Eperisone HCl matrix pellet formulations

The physicochemical characteristics of formulations were evaluated and the results of all formulation were mentioned in table 3.

Image analysis

Sphericity, Feret diameter and aspect ratio (AR) of all formulations are shown in table 4. The sphericity of formulations lies between 0.49-0.99. The aspect ratio of formulations lies in the range of 1.01-1.92. The value of the aspect ratio of pharmaceutical pellet must be less than 1.1 (Chatlapalli and Rohera 1998, Podczeck *et al.,* 1999, Thommes and Kleinebudde 2006, Maboos *et al.,* 2018, Nasiri *et al.,* 2019).

The surface characteristics as well as the morphology of coated pellet formulations are displayed in fig. 2a and fig. 3a. The shape of pellets is spherical and smooth which

Table 3: Evaluation of uncoated pellets formulations

Formulations code	Physical Evaluation						Chemical Evaluation
	Bulk Density (g/cm3)	Tapped Density (g/ cm3)	Carr's Index (%)	Hausner Ratio	Angle of Repose (θ0)	Friability (%)	Drug content Analysis (%)
F1	0.659	0.762	13.51	1.15	24.46	0.61	100.18
F2	0.668	0.771	13.35	1.15	25.45	0.55	99.43
F3	0.662	0.781	15.23	1.17	26.73	0.57	99.84
F4	0.674	0.761	11.43	1.12	25.34	0.49	98.66
F5	0.673	0.786	14.37	1.16	26.09	0.52	100.31
F6	0.684	0.813	15.86	1.18	27.72	0.47	100.13
F7	0.693	0.821	15.59	1.18	25.27	0.48	100.22
F8	0.682	0.774	11.88	1.13	25.62	0.45	100.15
F9	0.679	0.767	11.47	1.12	27.89	0.44	99.64
F10	0.675	0.761	11.30	1.12	28.14	0.38	101.33
F11	0.681	0.783	13.02	1.14	26.94	0.42	99.86
F12	0.673	0.765	12.02	1.13	25.67	0.39	100.21
F13	0.672	0.767	12.38	1.14	28.43	0.43	98.76
F14	0.677	0.764	11.38	1.12	28.14	0.35	99.43
F15	0.684	0.784	12.75	1.14	26.79	0.42	100.16
F16	0.682	0.771	11.54	1.13	27.81	0.32	100.24
F17	0.683	0.779	12.32	1.14	28.52	0.34	99.89
F18	0.685	0.786	12.84	1.14	25.61	0.28	100.43
F19	0.692	0.785	11.84	1.13	26.17	0.41	100.53
F20	0.681	0.769	11.44	1.12	28.14	0.26	101.61
F21	0.678	0.771	12.06	1.13	25.61	0.45	100.15
F22	0.684	0.774	11.62	1.13	27.51	0.39	98.24
F23	0.681	0.773	11.90	1.13	26.54	0.36	99.59
F24	0.692	0.785	11.84	1.13	27.67	0.44	100.21
F25	0.688	0.781	11.90	1.13	26.82	0.33	99.14
F26	0.691	0.801	13.73	1.15	25.54	0.31	99.86
F27	0.712	0.832	14.42	1.16	26.53	0.29	100.21
F28	0.692	0.834	17.02	1.20	26.28	0.36	98.76
F29	0.715	0.839	14.77	1.17	27.49	0.30	99.43
F30	0.705	0.842	16.27	1.19	25.61	0.28	100.16
F31	0.699	0.849	17.66	1.21	26.61	0.27	100.24
F32	0.691	0.834	17.14	1.20	26.76	0.45	99.89
F33	0.707	0.852	17.01	1.20	27.42	0.39	100.43
F34	0.717	0.863	16.91	1.20	27.87	0.36	98.76

shows film coating is smooth on the formulation. The cross-sectional image of formulation as shown in fig. 2b and 3b determines that particles form good matrix structure by coalescence.

Fourier transform infrared spectroscopy (FTIR)

FTIR technique is widely used for detection of any possible interaction of the drug with all excipients used in the formulation. The infrared spectra results showed that Eperisone HCl is compatible with all excipients used in the formulation as displayed in fig. 4a, 4b and 4c.

In vitro drug release studies

Effects of Polymers and Waxes on Drug Release

Formulations containing different types of polymers and waxes alone or in combination in different concentrations failed to prevent burst drug release from pellet formulation due to which drug release from pellets was not extended for 12 hours as shown in figs. 5, 6 and 7.

Effect of EC coating on matrix pellets

Matrix uncoated pellet failed to extend the drug release from formulation up to the desired time period. It was seen that by coating matrix pellets formulation F5 and F7 with 5% ethyl cellulose, drug release was controlled up to desired time period by forming a hydrophobic film around matrix pellet formulation. Thus, Eperisone HCl release from F5 and F7 matrix pellet formulation was successfully sustained up to 12h by coating with 5% ethylcellulose dispersion as shown in figs. 12 and 13.

Table 4: Image analysis of pellet formulations

Formulations code	Area (A)	Perimeter (*P*)	Feret diameter (mm)	Aspect ratio	Sphericity/ Shape factor
F1	6643	289.027	95.885	1.06	0.93
F2	497732	2580.06	833.39	1.01	0.99
F3	12,975	457.073	154.311	1.41	0.70
F4	10,900	390.771	121.696	1.01	0.97
F5	12,522	411.942	133.765	1.05	0.91
F6	18,006	561.265	202.41	1.92	0.51
F7	162790	1636	586.12	1.39	0.81
F8	11,243	413.361	140.46	1.26	0.78
F9	12,758	415.931	133.417	1.09	0.75
F10	13,464	438.623	143.171	1.15	0.55
F11	78759	1167.05	359.84	1.22	0.82
F12	103305	1285.13	416.04	1.33	0.75
F13	25,230	626.354	234.196	1.69	0.59
F14	428359	2450.42	787.55	1.14	0.88
F15	95579	1176.62	385.02	1.25	0.80
F16	100608	1292	464.86	1.46	0.68
F17	437306	2531.03	811.61	1.17	0.86
F18	114341	1281.78	422.30	1.26	0.80
F19	72728	1072.25	351.27	1.35	0.74
F20	107093	1351.88	399.81	1.15	0.87
F21	136780	1409.64	470.11	1.25	0.79
F22	13,067	419.126	133.135	1.04	0.72
F23	364907	2244.95	745.38	1.16	0.86
F24	130788	1365.73	452.99	1.25	0.80
F25	12,830	432.91	134.358	1.05	0.75
F26	12,868	417.443	133.544	1.04	0.72
F27	10,773	384.07	125.543	1.07	0.67
F28	13,513	431.267	150.881	1.23	0.54
F29	8801	355.000	110.725	1.02	0.74
F30	10,424	377.838	121.840	1.05	0.70
F31	13,464	438.623	143.171	1.15	0.55
F32	11517	404.16	130.973	1.09	0.79
F33	11553	393.681	130.648	1.09	0.67
F34	14422	444.383	155.003	1.30	0.49

Effect of dissolution medium on drug release

The dissolution profile of coated pellet formulations in different dissolution medium is shown in fig. 8,9, 10, 11, 12 and 13.

Drug release kinetics

The kinetics of coated formulations was investigated through DD solver (adds inn program of MS excel) as mentioned in table 5. The release kinetics was best described by Hixson Crowell kinetics having linearity range of R2 = 0.987-0.999.

Drug release mechanism

The release exponent "n" of all coated formulation was found to be in the range of 0.627 to 0.747 which indicates that the release mechanism of the drug was non-Fickian diffusion.

Stability studies

The shelf life was determined by using software Stab version 3.9. The shelf life of the F5 coated formulation was 20 months.

DISCUSSION

Sustained release pellets of Eperisone HCl (high water-soluble drug) were prepared through extrusion and spheronization technique using different hydrophobic and hydrophilic matrix formers like HPMC K4M, HPMC K15M, EC (7cps), Carnauba wax, Compritol ATO 888 and Glyceryl monostearate (10%). Microcrystalline and GMS was used as spheronizing aid in formulations. Maboos *et al.,,* reported GMS and MCC as a good spheronizing aid (Maboos *et al.,* 2018). The effect of different hydrophobic and hydrophilic matrix formers was determined on pellets sphericity and release behaviour of

Table 5: Drug Release Kinetics of Coated Formulations

Formulations code	First Order		Zero Order		Higuchi		Korsmeyer-peppas			Hixson-Crowell		Baker-Lonsdale	
	R^2	$k1(hr^{-1})$	r^2	$k\ (hr^{-1})$	r^2	$kH(hr^{-1/2})$	r^2	n	$kkp(hr^{-n})$	R^2	$kHC(hr^{-1/3})$	R^2	$kbl(hr^{-1})$
0.1 N HCl pH 1.2													
F1	0.958	0.331	0.851	17.587	0.897	35.842	0.963	0.701	27.415	0.987	0.093	0.803	0.032
F2	0.984	0.260	0.826	13.409	0.946	31.497	0.990	0.653	24.719	0.999	0.073	0.859	0.025
F3	0.977	0.192	0.892	10.360	0.922	27.020	0.986	0.704	18.668	0.993	0.054	0.840	0.018
F4	0.977	0.198	0.883	10.506	0.927	27.439	0.986	0.693	19.336	0.993	0.055	0.844	0.018
F5	0.977	0.150	0.937	8.383	0.913	23.842	0.994	0.747	14.536	0.994	0.042	0.835	0.013
F7	0.976	0.155	0.928	8.522	0.919	24.278	0.993	0.732	15.260	0.993	0.044	0.839	0.014
Phosphate buffer pH 4.5													
F1	0.963	0.353	0.819	18.101	0.918	37.015	0.970	0.669	29.553	0.992	0.098	0.821	0.035
F2	0.985	0.274	0.787	13.688	0.957	32.250	0.990	0.627	26.366	0.997	0.076	0.870	0.026
F3	0.982	0.202	0.859	10.575	0.938	27.697	0.987	0.670	20.380	0.993	0.057	0.857	0.019
F4	0.980	0.210	0.851	10.760	0.943	28.209	0.989	0.662	21.067	0.993	0.058	0.859	0.020
F5	0.974	0.164	0.914	8.763	0.928	25.021	0.993	0.713	16.336	0.992	0.046	0.845	0.015
F7	0.971	0.169	0.916	8.906	0.929	25.427	0.995	0.714	16.591	0.991	0.047	0.843	0.016
Phosphate buffer pH 6.8													
F1	0.965	0.344	0.819	17.850	0.915	36.496	0.968	0.670	29.105	0.992	0.096	0.822	0.033
F2	0.984	0.267	0.810	13.557	0.952	31.888	0.991	0.641	25.500	0.998	0.074	0.864	0.025
F3	0.980	0.198	0.877	10.482	0.930	27.396	0.987	0.687	19.536	0.994	0.055	0.848	0.018
F4	0.978	0.205	0.866	10.657	0.936	27.892	0.987	0.675	20.304	0.993	0.057	0.852	0.019
F5	0.974	0.160	0.927	8.689	0.921	24.762	0.994	0.730	15.626	0.994	0.045	0.838	0.015
F7	0.970	0.172	0.909	9.003	0.931	25.729	0.994	0.706	17.054	0.990	0.048	0.844	0.016

Eperisone HCl from pellet formulations. The burst release was observed in all matrix pellet formulations which indicated that different hydrophobic and hydrophilic matrix formers alone or in combination failed to control drug release up to desired time period. It was seen that by coating matrix pellets formulation F5 and F7 with 5% ethyl cellulose, drug release was controlled up to the desired time period by forming a hydrophobic film around matrix pellet formulation. Ethyl cellulose of high viscosity grade is widely used in drug microencapsulation as it is proven to produce durable and stronger films (Chhipa *et al.,* 2009). Ethyl cellulose has good solubility in aliphatic alcohols and having no solubility in water (Chemical 2013), therefore IPA and water in 9:1 ratio were used as a solvent for preparation of 5% EC coating dispersion. In the present work, Ethyl cellulose 10 cps was selected as it forms stronger film having good adhesion property around the cores because of its high molecular weight as film from this viscosity grade have reduced free volume because it forms a greater number of entanglements, which results in decreased transport of drug through polymer layer. The release of drug in F5 and F7 coated formulation was controlled which indicates that Eperisone HCl release from both formulations was pH-independent. Muschert *et al.,* determined that drug release from ethylcellulose coated pellets was not dependent on pH (Muschert *et al.,* 2009).

The infrared spectra results showed that Eperisone HCl is compatible with all excipients used in the formulation. The sphericity of pellet formulations lies between 0.49-0.99. The aspect ratio of formulations lies in the range of 1.01-1.92. The pellet formulation containing HPMC K15M produce dumbbell shaped pellet with less percentage yield. The value of the aspect ratio of pharmaceutical pellet must be less than 1.1 (Chatlapalli and Rohera 1998, Podczeck, Rahman *et al.,* 1999, Thommes and Kleinebudde 2006, Maboos *et al.,* 2018, Nasiri *et al.,* 2019). The pellets shape of F5 and F7 coated formulation is spherical and smooth which shows film coating is smooth on the formulation. The cross-sectional image of F5 and F7 coated pellet formulation determines that particles form good matrix structure by coalescence.

The mechanism of drug release of all coated formulation was non-Fickian diffusion. The value "n" was a function of the physicochemical property of the drug and polymer. However, swelling of the coated formulation occurs as soon there is contact with the dissolution medium resulting in the dissolution of the drug which is present inside the polymer coat and finally it permeates from the polymer coat. Moreover, swelling of the polymer coat continues until there is an establishment of equilibrium between the hydration and polymer elastic strength.

The stability of F5 coated pellet formulation was determined on accelerated conditions as per ICH guidelines. The results of stability data had shown that physical appearance, % drug content, and dissolution were not changed significantly indicating that formulation remained stable over time.

CONCLUSION

The results had shown that hydrophobic (polymeric based and wax-based) and hydrophilic (polymeric based) matrix

former alone or in combination unable to extend the release of Eperisone HCl up to the desired time period. The initial burst release of Eperisone HCl (BCS class I drug) from matrix pellet formulations were prevented by coating with 5% EC dispersion. The drug release from F5 and F7 coated formulation was sustained for up to 12 hours. The mechanism of drug release for coated pellet formulations was non-Fickian diffusion. No drug and excipient interaction were observed as proven by FTIR results. Thus, coating with 5% EC (ethylcellulose) dispersion was proven to extend the release of Epersioen HCl (high water-soluble drug) up to the desired period of time. The developed sustained-release pellet of Eperisone HCl can effectively be used in the treatment of musculoskeletal disorders because it improves the patient compliance, reduces the dosing frequency, minimizes plasma fluctuation level and will increase the bioavailability as compared to the immediate-release tablet of Epersione HCl.

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