Omdurman Journal of Pharmaceutical Sciences

https://journal.oiu.edu.sd/index.php/ojps

Formulation and Evaluation of Diclofenac Sodium in Different Transdermal Drug Delivery Systems

Israa Omerelfaroug Elhassan[1*], Hana Kamal Omer [2], Samra Ismail Yousif[3], Lamia Abdalla Gadien[4], Eltayeb Suliman Elamin[5]

[1, 2,3,4,5] Department of pharmaceutics, Faculty of pharmacy, Omdurman Islamic University

[*] corresponding author, Tel: +249928794088

Email: *sarroya93@hotmail.com*

DOI 10.52981/ojps.v2i2.2171 ISSN: 1858-506X

Abstract

Diclofenac sodium is found in different topical dosage forms which varied in their percuetanus absorption and hence in their therapeutic effect. In this study, three different formulations gel, emulgel and cream, containing 1% diclofenac sodium were developed in order to compare their permeation through rabbite skin using franz diffusion cells. They were subjected to various evalution tests such as physical appearance and rheological behavior. Menthol was added to the prepared formulations in a quanitity of about 1% , as permeation enhancer, and the enhancement in permeability was assessed. Carbopol gel, aqueous cream and emulgel showed acceptable results concerning color, spreadabilty, and homogenisity. The results showed that the cumulative amount of diclofenac sodium that permeated from the prepared formulations in this order gel > cream > emulgel. The addition of menthol to the formulation resulted in an increase in the amount of drug permeated. The study emphasized that optimization of the type of transdermal dosage forms and the addition of a peneteration enhancer can be resulted in an acceptable permeated amount of diclofenac sodium through the skin.

Key words: *Diclofenac sodium, Cream;Emugel;Gel, Peneteration enhancement and Transdermal delivery systems.*

1. Introduction

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAIDs), frequently used in managing pain and symptoms of inflammatory and rheumatic diseases because of its good efficacy. Although, it is associated with worrying cardiovascular side effects and serious gastrointestinal events [1]. Therefore, to avoid and decrease its gastrointestinal side effects it is recommended to use gastro- protective dosage forms or change the route of administration [2]. The evidence-based reviews and clinical studies showed that the topical diclofenac preparations are as effective as oral preparation in the treatment of various inflammatory conditions with a good safety profile and less systematic side effects [1-3] It is well-known that the diclofenac sodium has difficulties to permeate through skin, many approaches have been developed to overcome this limitation such as using more lipophilic salts like using diclofenacdiethyl amine which permeated 2-4 folds larger than other salts of diclofenac, improve the vehicle composition and occlusion or adding permeation enhancers [4,5].

Numerous experiments have suggested that the formulation and the vehicle composition can alter the permeation of the drug molecule [6]. Sanna et al. studied the influence of the composition of the formulation on diclofenac sodium release rate, their results showed that the release of diclofenac was affected largely by the vehicle and excipients used [7]. There are many available topical formulations in the markets that may be varied in their permeation profile [8].Therefore, it is important to compare the formulations and in order to display the influence of the composition of the dosage form on the permeation of diclofenac sodium through the skin and also to guide the selection of the best dosage form for transdermal drug delivery [9].

Permeation enhancers have shown growth in their popularity in the recent years as an effective tool to improve the drug absorption through the skin. Solvents, surfactant, urea and its derivatives are an example of chemicals that are documented to have an enhancing effect on the skin [5]. However, these chemicals may cause many adverse effects hence restrict their use until safety profile established [10]. Presently, many studies focused on naturally occurring chemicals such as terpenes which presents good enhancing effect including menthol on many drugs such as indomethacin, nifedipine propranolol tetracaine and diclofenac sodium [11-15]

Thus the objective of this study was to formulate and evaluate diclofenac sodium (1% w\w) in three semi-solid dosage forms , gel, cream, and emulgel; and then to conduct in vitro permeation study in

order to compare them. In addition, the effect of 1% menthol on permeation from prepared dosage forms was examined.

2. Materials and Methods:

2.1 Materials:

Tween 20 was purchased from (Labtech Chemicals, india). Diclofenac sodium, Carbomer 940, propylene glycol, Cetostearyl Alcohol, Triethanolamine, Methyl paraben, Propyl parabenand L-menthol Glycerin were purchased from (Shin Poong Pharm.co., ltd, Korea). Span 20 was purchased from (Sigma, USA), Liquid paraffin and White soft paraffin were purchased from (local market, Sudan). Sodium carboxymethylcellulse (Na CMC) was purchased from(Alfa Aesar-Johnson Matthey company and heysham-lancs). Hydroxypropylmethylcellulose (HPMC) was purchased from (central Drug House(ρ) Ltd, India).

2.2 Methods

2.2.1. Preparation of Diclofenac Sodium cream containing span and tween Cream (DS-STC)

The required quanitity of each ingredient was weighed accurately with sensitive balance Cetostearyl alcohol was melted in 57° C in water bath, then span 20 was dissolved in the liquid paraffin while tween 20 was dissolved in a part of distilled water. white soft paraffin and liquid paraffin were added to cetostearyl alcohol and mixed together, and then the mixture of water with tween 20 was added at the same temperature with continues stirring. After that diclofenac sodium was dissolved in the remaining water and dispersed into cream by stirring. The prepared creams were signed (DS-STC1,DS-STC2 and DS-STC3) and kept at suitable containers for further use.

Table 1 Ingredients of DS-STCs.

Formula (No) **Ingredients (%w/w)**	**DS-STC1***	**DS-STC2**	**DS-STC3**
Diclofenac sodium	1	1	1
Cetostearyl alcohol	8	8	8
Liquid paraffin	6	6	6
Span 20	4	2.3	3.2

12qw Tween 20	6	2.7	3.8
White soft paraffin	5	15	15
Distilled water up to	100	100	100

* DS-STC, Diclofenac sodium cream containing Span 20 and tween 20.

2.2.2. Preparation of Diclofenac sodium aqueous cream BP(DS-AC)

Table 2 Ingerdients of dicolfenac sodium aqueous cream (DS-AC)

Ingredients	**Amount (%w/w)**
Emulsifying ointment	30
Methyl paraben	0.1
Propyl paraben	0.01
Diclofenac sodium	1
Distilled water up to	100

*DS-AC Diclofenac sodium aqueous cream BP

Methyl paraben and propyl paraben were dissolved in small amount of distilled water heated at heat at 57° C. The emulsifying ointment was melted at 57° C in water bath, and then the solution of methyl and propyl paraben were added at the same temperature and the mixture was stirred. Diclofenac sodium was dissolved in small amount of distilled water and added to the mixture, the water was added to produce 100 gm final weight. Finally, the cream was homogenized with mortar and pestle to produce smooth cream. The prepared cream was assigned (DS-AC) and kept at a suitable container for further use.

2.2.3. Preparation of diclofenac sodium gels

Table 3.Ingredients of diclofenac sodium gels

Ingredients(% w/w)	DS-CMG	DS-HPG	DS-CAG
Diclofenac sodium	1	1	1
Na CMC	3	-	-
HPMC	-	3	-
Glycerin	-	15	-
Carbopol 940	-	-	1
Propylene glycol	-	-	40
Triethanolamine	-	-	1.1
Methyl paraben	0.1	0.1	0.1
Propyl paraben	0.01	0.01	0.01
Distilled water up to	100	100	100

*DS-CMG Diclofenac sodium Na CMC gel
*DS-HPG Diclofenac sodium HPMC gel
*DS-CAG Diclofenac sodium carbopol 940 gel

Na CMC) gel was prepared by dissolving diclofenac sodium in distilled water, followed by an addition of the required amount of Na CMC under constant stirring. For preparation of HPMC gel, 1 gm of diclofenac sodium was dissolved in 15 ml of glycerin with the mild heat. The HPMC K100M was added to 75 ml of distilled water and stirred until dissolved. Then the two mixtures were mixed and the water was added up to 100 gm. For preparation of Carbopol 940 gel, menthyl paraben, propyl paraben and diclofenac sodium were dissolved in the mixture of water and propylene glycol. Carbopol was dispersed in this mixture and kept under continuous stirring, and then the mixture was put in the homogenizer to insure good dispersion of carbopol. The resulting gel was neutralized by the addition of triethanolamine. The prepared gels were assigned (DS-CMG, DS-HPG and DS-CAG) kept at suitable containers for further use.

2.2.4. Preparation of diclofenac sodium emulgel (DS-EMG)

Table 4 Ingredients of diclofenac sodium emulgel (DS-EMG)

Ingredients	**Amount (%w/w)**
Diclofenac sodium	1
Liquid paraffin	5
Tween 20	1
Span 20	1.5
Propylene glycol	5
Methyl paraben	0.1
Propyl paraben	0.01
Carbopol 940	1
Tiethanolamine	q.s
Distilled water up to	100

*DS-EMG Diclofenac sodium emulgel

The emulgel was prepared in three steps; firstly, the gel was prepared as follow, Carbopol 940 was dispersed in the distilled water with constant stirring, then the pH was adjusted using triethanolamine; secondly, the emulsion was prepared as follow, the oil phase of the emulsion was prepared by dissolving Span 20 in liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in distilled water. Methyl and propyl parabens and diclofenac sodium were dissolved in propylene glycol, and both solutions were mixed with the aqueous phase. The oil and aqueous phases were separately heated to 70°C; then the oily phase was added to the aqueous phase with continuous stirring until the mixture was cooled to room temperature. In the final step, the emulsion was mixed with the gel with gentle stirring to obtain the emulgel. The prepared emulgel was assigned (DS-EMG) and kept at a suitable container for further use.

2.2.5. Preparation of dosage forms containing menthol

The required quanity of Menthol (1%w/w) was added to the formulation as follow, dissolved in emulsifying ointment in the case of cream, or propylene glycol when preparing carbopol 940 gel or liquid paraffin for the emulgel. Then all the steps for preparation were done as above. Each formulation containing menthol was assigned by addition of MT at the end of its code.

2.2.6. Characterization of prepared formulations

2.2.6.1. Washability test

Small amount of each formulation was applied to the back of hand and time needed for complete removal of the preparation by tap water was recorded.

2.2.6.2. Appearance and physical examination

All prepared formulations were tested for homogeneity by visual inspection after the formulations had been set into their containers. They were tested for their color, appearance, homogeneity, liquefaction and phase separation.

2.2.6.3. pH test

A quantity of about 2.5 gm of each prepared formulation was weighed in a beaker, dissolved in 100 gm of distilled water and then the pH measured by using digital pH-meter (pH /temperature bench meter. Mi150). The pH of each sample was evaluated in triplicate.

2.2.6.4. Spreadability

The spreadability of the formulation was measured using apparatus recommended by Multimer et al,.1956 [16]. The apparatus consists of two glass slides (7.5 × 2.5 cm), one of which was fixed onto the wooden board and the other was movable, tied to a thread which passed over a pulley, carrying a weight. One gm of each prepared formulation was placed between the two glass slides. 100 gm weight was allowed to rest on the upper slide for 1 to 2 minutes to expel the entrapped air between the slides and to provide a uniform film of the formulation. The weight was removed and the top slide was subjected to a pull obtained by attaching 30 gm weight over the pulley. The time required for moving slide to travel premarked 6.5 cm distance was noted. The readings obtained could indicate the relative spreadability of different formulations. The spreadability of each sample was evaluated in triplicate.

2.2.6.5. Permeation study

The permeation studies were performed using the franz diffusion cell apparatus with the side arm and external jacket (SES GmbH-Analyses system, Germany) and thermostat (ThermoFisher Scientific, Newington). Rabbit skin were placed between the donor and receptor chambers of the cell with the dermal side in contact with the receptor medium. The receptor chamber was filled with 5.1 mL of phosphate buffer (pH = 7.4) and kept at 37 ± 0.5 ◦C using a circulating water jacket. The receptor sampling side arm opening was carefully covered with Parafilm to avoid evaporation of the water from the receptor medium. Then 1 gm of each prepared formulation was applied on the skin. Samples of 0.5 ml were withdrawn from the middle of the receptor compartment, using 5 ml syringe, at 2, 4, and 6 hr and replaced with the same volume of phosphate buffer. The presence of air bubbles were carefully

checked after each medium replacement. The permeation studies were performed in two cells for each formulation to decrease the errors. Samples were stored in the refrigerator (5 ◦C) until the HPLC analysis. The cumulative drug amount permeated at each sampling time was calculated.

2.2.6.6. HPLC measurements

The HPLC system (SHMADZU CORPORATION, Japan) was used. Sample aliquots (20 µL) were injected onto an InerSustain C18 column (4.6 × 150 mm, 3.5 m) (SHMADZU CORPORATION, Japan) and an absorbance of 280.16 nm was monitored. The system was run with a mobile phase consisting of methanol: 0.1% v/v formic acid in a ratio of 75:25 (v/v). A flow rate and injection volume of 1 mL/min and 20 µL were used respectively. The observed retention time of diclofenac was 3.9-4.5 min. The mobile phase was filtered through a 0.24 m Nylon filter and degassed in an ultrasonic bath for 30 min before use. The column was maintained at 37 ◦C during the run and then washed with water followed by acetonitrile after each use.

3 Results and discussion

3.1 Appearance and physical examination

Table 5 Results of appearance and physical examination of diclofenac sodium formulations

Formulation code	Color	Homogeneity	Phase separation
DS-STC1	White	*	Yes
DS-STC2	White	*	Yes
DS-STC3	White	*	Yes
DS-AC	White	***	None
DS-HPG	Transparent	*	None
DS-CMG	Transparent	**	None
DS-CAG	Transparent	***	None
DS-EMG	White	***	None
DS-AC-MT	White	***	None
DS-CAG-MT	Transparent	***	None

*: poor **: good ***: excellent

As shown in table5, creams containing span 20 and tween 20 and HPMC gel of diclofenac sodium showed poor homogeneity. Na CMC gel of dicolfenac sodium had good homogeneity but it was very sticky. In addition, span 20 and tween 20 creams were unstable and showed phase separation problem, this may be due to incorrect selection of emulsifying agents or presence of

incompatible excipients [17]. Hence, these formulations were discarded and not further used. The other formulations showed smooth and homogeneous appearance with no phase separation problem therefore they were considered for further study.

3.2 pH, spreadability and washability

Table 6. Results of pH, spreadability and washability selected diclofenac sodium formuations

Formulation	Ph	Spreadability (g.cm/sec)	Washability (sec)
DS-AC	7.70	39	5
DS-AC-MT	7.35	59	6
DS-EMG	7.10	52	3
DS-EMG-MT	7.12	45	4
DS-CAG	7.44	52	2
DS-CAG-MT	7.44	48	2.3

As shown in table 6, the pH values ranged from 7.10 to 7.70, which were considered acceptable, which wouldn't develop irritation when applied to the skin. The delivery of the correct dose of the drug depends highly on the spreadability of the formulation. The rate of spreading also depends on the viscosity of the formulation, the rate of evaporation of the solvent, and the rate of an increase in viscosity with the concentration that results from evaporation. Increasing the viscosity of the delivery vehicle increases its retention time at the target site but also decreases its spreadability [18]. All the formulations showed acceptable spreadability. But in comparison the prepared gels and emugels showed higher spreadability than creams. The results might be attributed to the different in viscosity and lipid content of these formulations. The effect of menthol addition to the formulation showed the diverse effect, it an increased the cream spreadability by more than 60% while in emulgel decreased the spreadability by 13% and in gel decreased by 7% . These results might indicate that menthol addition had great effect on the consistency of the formulation.

All prepared formulations showed acceptable values of washability which might be suitable for patient use. Gel was more washable than emugel, emugel more than cream. Menthol addition showed a decrease in washability of all prepared formulations. These results might be contributed to the lipid content of the formulation. The highest

lipid cotent formulation associated with lowest washability, need long time to washout [19].

3.3 Permeability study

The cumulative amount penetrated form each formulation through rabbit skin was determined after 6 hours, it was observed that the cumulative amount of the drug was in this order gel > cream > emulgel. This result was consistent with Patel et al.[20], who stated that the gel has better release of the drug irrespective of the water solubility of the drug [20]. This unexpected result can be explained by the high content of the permeation enhancer, propylene glycol in the gel base as co-solvent, which may has also affected the thermodynamic activity of the vehicle by altering the solubility of diclofenac sodium and modified the stratum cream structure and consequently increased the drug permeability [21,22]. On the other hand, emulgel had the lowest penetration through skin, but theoretically the emulgel was expected to be better than cream

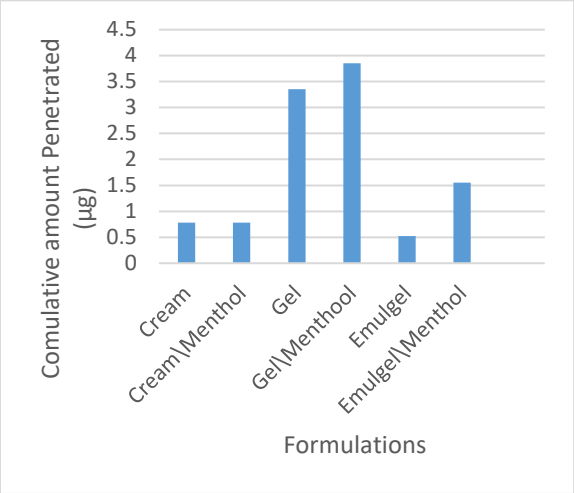

Figure 1. Cumulative amount penetrated after application of different diclofenac sodium formulations

and gel, because the composition of the emulgel base is similar to that of gel, and in addition it contains nonionic surfactants which are good permeation enhancers [23]. Conversely, the cream showed better penetration than emulgel, the explanation for this is the using of anionic surfactants which may cause greater enhancement but, also can damage the skin more than nonionic surfactants [23].

With regard to these results, we can see that the permeation profile of diclofenac sodium from the different vehicles was unpredictable. Therefore, the permeation profile of each dosage form from any drug may need to be assessed to help the picking up and select the best vehicle which may give the desired therapeutic effect form the different dosage forms in the market. Beside this, it could also help when designing transdermal

delivery systems to suitably choose additives and the type of vehicle.Thus the gel was found to be suitable for further development and assessment.

Menthol was extensively studied and used to enhance the penetration through the skin of many drugs because of its many advantages such as low tendency to irritate the skin and a low concentration of menthol is enough to give a significant enhancement [13]. In addition, menthol used to increase the penetration of many drugs with a different water solubility [24]. In the present study, menthol showed enhanced effect on permeability for all prepared formulations and its effect was varied according to the type of formulation. Slight an increase in permeability of gel and cream formulations while a marked increase in permeability, more than 150%, of emugel formulation.

4 Conclusion

This study was conducted to compare the permeation of 1% diclofenac sodium from different transdermal dosage forms through rabbit skin. The carbopol gel showed the best permeation through the skin. And the addition of menthol to the vehicle may increase the permeability to some extent according to the type of formulation. The findings of this study emphasize that the type and composition of the vehicle used for drug formulation can affect its penetration through the skin and to select the best transdermal drug delivery systems for specific drug.

References

[1] Zacher J, Altman R, Bellamy N, Brühlmann P, Da Silva J, Huskisson E, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. *Curr Med Res Opin* [Internet]. 2008;24(4):925–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18279583

[2] Banning M. Topical diclofenac: clinical effectiveness and current uses in osteoarthritis of the knee and soft tissue injuries. *Expert Opin Pharmacother*. 2008;9:2921–9.

[3] Heyneman C a, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs*. 2000;60(3):555–74.

[4] Goh CF, Lane ME. Formulation of diclofenac for dermal delivery. *Int J Pharm* [Internet]. 2014;473(1–2):607–16. Available from: http://dx.doi.org/10.1016/j.ijpharm.2014.07.052

[5] Felton AL. *Remington Essentials of Pharmaceutics*. First edi. Pharmaceutical Press. London, UK: Pharmaceutical press; 2013. 772 p.

[6] Gibson M. *Pharmaceutical Preformulation and Formulation A Practical Guide from Candidate Drug Selection to Commercial Dosage Form*. Second edi .Gibson M, editor. America. Florida: by Interpharm/ CRC; 2004.

[7] Sanna V, Peana AT, Moretti MDL. Effect of vehicle on diclofenac sodium permeation from new topical formulations: in vitro and in vivo studies. *Curr Drug Deliv* [Internet]. 2009;6(1):93–100. Available

from: http://www.ncbi.nlm.nih.gov/pubmed/19418961

[8] Committee JF. *British National Formulary*. 67th ed. London: BMJ Group and Pharmaceutical Press; 2014.

[9] Stahl J, Wohlert M, Kietzmann M. The effect of formulation vehicles on the in vitro percutaneous permeation of ibuprofen. *BMC Pharmacol* [Internet]. 2011;11:12. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-83355164013&partnerID=tZOtx3y1

[10] Nokhodchi A, Sharabiani K, Rashidi MR, Ghafourian T. The effect of terpene concentrations on the skin penetration of diclofenac sodium. *Int J Pharm*. 2007;335(1–2):97–105.

[11] Levison KK, Takayama K, Isowa K, Okabe K, Nagai T. Formulation optimization of indomethacin gels containing a combination of three kinds of cyclic monoterpenes as percutaneous penetration enhancers. *J Pharm Sci* [Internet]. 1994;83(9):1367–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7830256

[12] Thacharodi D, Panduranga Rao K. Transdermal absorption of nifedipine from microemulsions of lipophilic skin penetration enhancers. *Int J Pharm*. 1994;111(3):235–40.

[13] Kunta JR, Goskonda VR, Brotherton HO, Khan MA, Reddy IK. Effect of menthol and related terpenes on the percutaneous absorption of propranolol across excised hairless mouse skin. *J Pharm Sci*. 1997;86(12):1369–73.

[14] Fang C, Liu Y, Ye X, Rong Z xing, Feng X mei, Jiang C bing, et al. Synergistically enhanced transdermal permeation and topical analgesia of tetracaine gel containing menthol and ethanol in experimental and clinical studies. *Eur J Pharm Biopharm*. 2008;68(3):735–40.

[15] Obata Y, Takayama K, Maitani Y, Machida Y, Nagai T. Effect of pretreatment of skin with cyclic monoterpenes on skin permeation of dicofenac in hairless rats. *Biol Pharm Bull* [Internet]. 1993;16(3):312–4. Available from: http://joi.jlc.jst.go.jp/JST.Journalarchive/bpb1993/16.312?from=CrossRef

[16] Bhalekar MR, Madgulkar AR, Kadam GJ, Road K, Near RTO. Evaluation Of Gelling Agents For Clindamycin Phosphate Gel. *World Journal Of Pharmacy And Pharmaceutical Sciences*. 2015;4(7):2022–33.

[17] Jones D. *FASTtrack Pharmaceutics-Dosage Form and Design*. First edi. London ● Chicago: the Pharmaceutical Press; 2008. 287 p.

[18] Garg A, Aggarwal D, Garg S, Singla AK. Spreading of semisolid formulations. *Pharm Technol*. 2002, 84–105.

[19] Aulton ME, Taylor kevin MG. *Aulton's pharmaceutics the design and manufacture of medicines*. fourth edi. Aulton ME, Taylor kevin MG, editors. Elsevier Ltd; 2013. 894 p.

[20] Patel H, Panchal MMS, Shah S, Vadalia KR. Formulation and Evaluation of Transdermal Gel of Sildenafil Citrate. *Int J Pharm Res Allied Sci*. 2012;1(3):103–18.

[21] Banker GS, Rhodes CT. *Modern Pharmaceutics*. fourth edi. NewYork • Basel: Marcel Dekker, Inc.; 2002.

[22] Arellano A, Santoyo S, Martín C, Ygartua P. Influence of propylene glycol and isopropyl myristate

on the in vitro percutaneous penetration of diclofenac sodium from carbopol gels. *Eur J Pharm Sci*. 1998;7(2):129–35.

[23] Arellano A, Santoyo S, Martn C, Ygartua P. Surfactant effects on the in vitro percutaneous absorption of diclofenac sodium. *Eur J Drug Metab Pharmacokinet*. 1998;23(2):307–12.

[24] Krishnaiah YSR, Satyanarayana V, Karthikeyan RS. Penetration enhancing effect of menthol on the percutaneous flux of nicardipine hydrochloride through excised rat epidermis from hydroxypropyl cellulose gels. *Pharm Dev Technol* [Internet]. 2002;7(3):305–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12229262